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THE EFFECT OF SUBCUTANEOUS INJECTIONS OF MAGNESIUM SULPHATE IN CHOREA*

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The existence of the condition termed chorea has been well known ever since the Middle Ages. For centuries the medical profession has endeavored to treat it satisfactorily, as well as to explain its etiology. The results so far have been disappointing. Sedatives, such as bromids and chloral, the salicylates, rest, hydrotherapy, and hygienic measures, all have a beneficial influence on certain symptoms in chorea. Arsenic, however, in this condition is a greatly overestimated drug; I have yet to see it relieve, even in the slightest degree, the choreic manifestations or shorten the course of the disease. We are still sadly in want of a specific remedy to cope satisfactorily with this annoying, chronic, and occasionally serious malady.

In the absence of positive knowledge as to the causation of chorea, it is justifiable to attempt symptomatic treatment alone, with the view of lessening the severity and frequency of the choreic manifestations and rendering the patient more comfortable. Stimulated by the work of Meltzer in the treatment of tetanus by injections of magnesium sulphate, I applied a similar method in a series of chorea cases, in the hope that a favorable influence would be exerted on the psychomotor system.

Meltzer investigated the effect of various salts on animals and human beings and found that of magnesium sulphate unmistakably inhibitory in character. Various modes of administration were investigated—intravenous, intraspinal, intramuscular, and subcutaneous. In intravenous and intramuscular injections the effect was rapid, but of short duration; in intraspinal injections, rapid and of longer duration; in subcutaneous injections, slow and of still longer duration, with the possibility of a cumulative action. Meltzer claims that in tetanus there is no other remedy capable of relieving the very severe convulsive symptoms so satisfactorily as the injection of magnesium sulphate. To explain the inhibitory phenomena exerted by magnesium sulphate in tetanus, he offers the hypothesis that the magnesium solution contained in the lymphatic circulation enters into the spaces, or, as termed by Sherrington, "synaptic membrane," between the various neurons or between neurons and muscle, and thus interrupts the passage of afferent

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impulses. He concludes that magnesium sulphate by subcutaneous injections should be given in every case of tetanus.

Chorea, though entirely dissimilar in etiology, in pathology, and in symptomatology to tetanus, is characterized by irregular, incoordinate muscular movements, which in turn depend on some pathologic condition of the psychomotor system, probably central in origin. Reasoning from analogy, therefore, I regarded it possible that magnesium sulphate might have a similar beneficial effect in chorea, and that a trial in a series of cases would be warranted. Feliziani and Natali have used intraspinal injections of magnesium sulphate in chorea with doubtful results. The latter had seven cases of chorea minor and one case of chronic chorea in which this method of therapy was employed. He claims that three patients were entirely, and four nearly, cured, but that the chronic case was not modified. Even if this method of therapy were but empirical and had not a possible theoretical foundation, no apology would be necessary for employing it in an endeavor to find a remedy for this obscure condition which has for so long baffled medical science. That the results were disappointing in chorea does not in any way speak against the use of magnesium sulphate in tetanus, in which disease excellent results have been obtained. If chorea is a direct sequel of rheumatism, influenza, scarlatina, or other infections, it is possible that no remedy will be of any avail until the respective toxins have been thoroughly eliminated from the system in each case, and the damage done to the nervous system healed by the natural and gradual processes of repair.

METHOD AND TECHNIC OF INJECTION

Five successive patients with chorea from the children's service of Dr. Koplik at Mt. Sinai Hospital were treated by repeated subcutaneous injections of magnesium sulphate. In every case a 25 per cent. sterile solution was used. The dose ranged from 0.01 gm. magnesium sulphate per kilogram of body weight (that is, 0.04 c.c. of the 25 per cent. solution) at the beginning of treatment, with a daily increase to 0.2 gm. magnesium sulphate per kilogram of body weight (that is 0.8 c.c. of the 25 per cent. solution) at the termination of treatment. The actual amounts of solution used daily were from 3 to 30 c.c. The injections were given three times daily for from ten to fifteen days, with the ordinary record syringe, into the back, loins and buttocks of the patients.

EFFECT OF TREATMENT

The table gives in brief the important data regarding the cases under observation. In only one of the five patients treated by this method was there a marked improvement after the series of injections, and in this case the choreic movements gradually diminished, the child

became less irritable and general improvement was noted. It is very questionable whether or not the improvement was directly due to the treatment; it is possible that it was purely coincidental and the result of natural processes. In the four other cases there was no improvement, the magnesium sulphate having had apparently no effect whatever on the psychomotor system. In all events the results of the treatment in the small series of cases was not sufficiently promising in my opinion to justify a continuation of the treatment.

DATA OF FIVE PATIENTS TREATED FOR CHOREA BY MAGNESIUM SULPHATE

Name	Age, Yrs.	Duration before Admission, Wk.	Severity	Dose $MgSO_4$ per Kg. Body Weight, Gm.	Period, Days	Number of Injections	Results
A. L.	8	3	Moderate	0.01 to 0.2	11	44	No improvement
I. D.	5	2	Severe	0.01 to 0.055	11	40	Slight improvement
B. K.	9	5	Moderate	0.02 to 0.2	13	45	No improvement
E. O.	10	6	Severe	0.01 to 0.05	11	37	Considerable improvement
E. W.	10	1	Mild	0.01 to 0.2	11	44	Slight improvement

* All the patients were girls.

There are, however, certain decided objections to the use of this method. The quantity of solution used, especially at the termination of treatment, is so large that there is a possibility of an inflammatory reaction, even abscess formation. We did not have any accident of this nature, however, in our cases. Occasionally the patients, especially if very young, are likely to be unduly excited by the treatment itself. Another disadvantage is the possibility of having the needle broken off in the tissues during the administration of the solution, on account of the marked restlessness of the patient. Albuminuria has been reported by several observers after the injection of magnesium sulphate. In our cases albumin was noticed in several instances, but this condition disappeared after a short interval. This treatment, even if effective, would be best employed in hospitals, inasmuch as three or four injections daily by skilled hands would be required.

CONCLUSIONS

Subcutaneous injections of magnesium sulphate, though employed in only five cases, did not produce sufficient improvement to justify further trial.

I take this opportunity to thank Dr. L. G. Shapiro, formerly house physician of Mt. Sinai Hospital, for his painstaking assistance in this work.

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A STUDY OF NORMAL AND PATHOLOGIC CEREBROSPINAL FLUIDS IN CHILDREN *

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INTRODUCTION

This investigation has been undertaken to determine the relative value of various methods in use in the examination of the cerebrospinal fluid in sundry affections of the central nervous system of children.

The differentiation of true meningitis from serous meningitis by means of the cell content of the cerebrospinal fluid has been established by the introduction of lumbar puncture. Furthermore, the causative organism in various types of meningitis has been demonstrated by bacteriologic methods. It was at first believed that a diagnosis of tuberculous meningitis might be established by a characteristic increase in the number and type of cells found in the fluid, but it was later shown that the number of cells in this condition is subject to wide variation, and that there are a number of conditions which give the same cytologic findings, namely, encephalitis, acute anterior poliomyelitis, meningismus, syphilis of the central nervous system and tuberculous meningitis. In the last-named condition, then, we must have the added test of demonstrating tubercle bacilli in the cerebrospinal fluid to establish a diagnosis. This is possible in a large percentage of cases, but not invariably so.

Owing to the fact that clinical manifestations and microscopic findings in the cerebrospinal fluid in certain affections of the central nervous system were not adequate for ascertaining the nature of the process, the necessity for chemical and serologic methods of examination was obvious. This led to the development of methods for the qualitative determination of globulin in the cerebrospinal fluid by Nonne,[1] Ross-Jones,[2] Pandy,[3] and Noguchi.[4] These methods have all been advanced as an aid in the diagnosis of syphilitic affections of the central nervous system. Each has its distinct value as a means of

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1. Nonne: Syphilis and the Nervous System, p. 341.
2. Ross-Jones: Brit. Med. Jour., 1909, i, 1111.
3. Pandy: Neurol. Centralbl., 1910, xxix, 915.
4. Noguchi: Serum Diagnosis of Syphilis, Ed. 2, p. 155.

determining the presence of globulin, which is found in the cerebrospinal fluid in a number of conditions, and is generally conceded to be the result of and indicative of some inflammatory process affecting the meninges. The various tests showing the presence of globulin do not give any selective reaction, but vary somewhat in delicacy, and their intensity is dependent on the degree of inflammatory involvement. The exudation of globulin in the cerebrospinal fluid is usually accompanied by an exudation of cells, but globulin is not infrequently present without an increase of the latter. The application of the Wassermann reaction to the cerebrospinal fluid in syphilis of the central nervous system has proved invaluable.

In 1912 Lange[5] introduced the colloidal gold reaction, the specific significance of which is now well recognized by a large number of observers, although the exact nature of the reaction is still somewhat uncertain. Among the more recent publications on this subject, one by Miller[6] and his co-workers gives an exhaustive treatise on the development of the colloidal gold reaction from the early experiments of Zsigmondy to the practical application of this work as a diagnostic method in examination of the cerebrospinal fluid by Lange. Since its introduction observations on the gold chlorid reaction have accumulated from many sources. A summary of these leads us to conclude that there is a specific reaction in a pathologic cerebrospinal fluid, and that the test is a valuable adjunct to the present laboratory and clinical methods. The reaction is dependent on the presence of protein substances, and like the various globulin tests, is indicative of an inflammatory process in the meninges. However, it is not to be questioned that the reaction is to a certain extent selective, because of the uniform evidence of a specific reaction given by syphilitic cerebrospinal fluids, more particularly those from patients with general paresis.[7]

The test is generally conceded to be more delicate than the Wassermann reaction on the cerebrospinal fluid, when the reaction (precipitation of the colloidal gold) occurs in the so-called "syphilitic zone."[8] There has been no selective reaction observed in nonsyphilitic conditions and it is concluded that the test has no specific diagnostic import in many obscure affections. The occurrence of a positive reaction, however, does indicate a pathologic cerebrospinal fluid.

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5. Lange: Zentralbl. f. Chemotherapie, 1912, i, 44; Berl. klin. Wchnschr., 1912, xlix, p. 667.

6. Miller, Brush, Hammers and Felton: Bull. Johns Hopkins Hosp., 1915, xxvi, 391.

7. For the bibliography and summary of this subject, the reader is referred to the work of Miller, Brush, Hammers and Felton, Footnote 6.

8. Solomon, Koefod and Welles (Boston Med. and Surg. Jour., 1915, clxxiii, 956) consider the term "syphilitic zone" a misnomer, because of a number of different conditions giving reactions in the lower dilutions.

The occurrence of a substance in the cerebrospinal fluid which reduces Fehling's solution has been considered of diagnostic import because of its absence in various types of meningitis. Schloss[9] has published evidence to show that this reducing substance is dextrose and that the quantity varies within a relatively wide range in normal fluids and may be normal in quantity or decreased in tuberculous meningitis. Its absence in fluids from patients with purulent meningitis is well known. Most observers agree that this reducing substance is present in all clear fluids, hence its mere qualitative determination can have little significance in diagnosis.

The reduction of potassium permanganate by the organic substances of the cerebrospinal fluid has been utilized as a diagnostic method by Mayerhofer[10] and Neubauer[11] and has been mentioned as an aid to diagnosis in a case report by Lackner and Levinson.[12]

The amount of tenth-normal potassium permanganate reduced by 1 c.c. of cerebrospinal fluid is considered as the reduction index of the fluid. Hoffman and Schwartz[13] found that normal fluids, or fluids from patients presenting meningeal symptoms without actual inflammation of the brain or meninges, give low permanganate indexes (2 c.c. and less), and that borderline indexes (from 2 to 2.5 c.c.) occur in the early stages of an inflammatory process. They conclude that the reduction index has a distinct value in the examination of the cerebrospinal fluid.

TESTS SELECTED—TECHNIC

The routine examination of the cerebrospinal fluids in this work included the cell count, the determination of globulin by the methods of Nonne and Noguchi, the reduction of Fehling's solution, the reduction index of potassium permanganate, and the colloidal gold test. The Wassermann test was made only on those fluids in which there was some definite indication.[14] All fluids containing blood were rejected.

1. Cell Count: The cells were counted in the Thoma-Zeiss chamber. The pipet was rinsed with glacial acetic acid before filling with the fluid, to facilitate the differentiation of the nuclei. In a number of fluids a mixture of equal parts of glacial acetic acid and Wright's stain was drawn up to the 0.1 mark in a white cell pipet, which was then filled with fluid. This method has no advantage over the simple acetic acid method.

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9. Schloss: Am. Jour. Dis. Child., 1916, xi, 1.
10. Mayerhofer: Wien. klin. Wchnschr., 1910, xxiii, 651.
11. Neubauer: Ztschr. f. Kinderh., 1911, iii, 2.
12. Lackner and Levinson: Arch. Pediat., July, 1915, xxxii, 508.
13. Hoffman and Schwartz: Arch. Int. Med., 1916, xvii, 293.
14. For this work I am indebted to Drs. Olmsted and Flexner of the Department of Internal Medicine.

2. Globulin: (*a*) The globulin test of Noguchi was made according to the original description, 0.2 c.c. of fluid was boiled with 0.5 c.c. of 10 per cent. butyric acid and reheated after the addition of 0.1 c.c. of 4 per cent. potassium hydroxid. (*b*) The test of Nonne was made by adding 1 c.c. of a saturated solution of ammonium sulphate to 1 c.c. of cerebrospinal fluid. The ammonium sulphate is added slowly, so that a definite line of contact is formed. This is allowed to stand for one minute and observations are made for a precipitation at the line of contact. It is then completely mixed and observations are again made.

3. Lange Reaction: The difficulties and sources of error in the technic of the preparation of the colloidal gold reagent have no place in the present discussion. Suffice it to say that these difficulties are not great enough to warrant the abandonment of the test as a routine of cerebrospinal fluid examination. The test itself may be made easily and rapidly. Ten dilutions of the cerebrospinal fluid are made with 0.4 per cent. sodium chlorid ranging from 1 to 10, 1 to 20, 1 to 40 and so on to 1 to 5,120, and 1 c.c. of each dilution is used. An eleventh tube containing 1 c.c. of 0.4 per cent. sodium chlorid serves as a control. To each tube 5 c.c. of the colloidal gold reagent is added. After from ten minutes to one hour the characteristic color changes appear; after this time there is intensification of the colors, and the readings are best made twelve to twenty-four hours after the beginning of the reaction. The reagent has a bright orange-red color and the changes which occur are to a red-blue, purple (violet), blue, pale blue, and colorless; the intensity of the color change is expressed, in recording, by the numerals 1, 2, 3, 4, and 5 respectively. This method of recording has been explained in other publications and is quite uniform for all observers.

5. Permanganate Index: To 1 c.c. of the cerebrospinal fluid in a suitable flask, 50 c.c. of double distilled water and 10 c.c. of dilute sulphuric acid (concentrated sulphuric acid 1 part, water 3 parts) are added and the mixture is heated to the boiling point. Ten c.c. of tenth-normal potassium permangante are added, and the boiling is continued for exactly ten minutes. At the end of this time 10 c.c. of tenth-normal oxalic acid is added; on the addition of this, the solution becomes clear and the excess of oxalic acid is titrated with tenth-normal potassium permanganate to a faint pink end-point. This result gives the amount of potassium permanganate which has been reduced by the fluid examined and is known as the reduction index. As a control, 50 c.c. of water with 10 c.c. of the dilute sulphuric acid must be treated in the same way to determine their reducing activity at the time used. This has varied between 0.6 and 1.2 c.c. of potassium permanganate

at different times and is subtracted from the index given by the cerebrospinal fluid. The difference represents the true reduction index of the fluid examined.

COMMENT

One hundred and nineteen fluids were examined from 100 patients, and in each case laboratory and clinical findings were carefully correlated. Without reference to the clinical diagnosis, evidence of pathologic change in the fluids examined may be summed up as follows:

	No. Examined	Positive	Per Cent.
Cell count	118	45 (pleocytosis)	38
Noguchi	119	53	44
Nonne	119	32	27
Lange	119	71	60
Wassermann reaction	54	15	28
Fehling's	118	19 (negative)	16
Permanganate index	110	80 (more than 2)	72

The occurrence of globulin in the cerebrospinal fluid together with an increase in the cell content is undoubted evidence of an inflammatory process affecting the meninges, and pleocytosis, the Noguchi reaction, and the Nonne reaction show a close relation, though it is evident that the Noguchi globulin test is far more delicate than that of Nonne. In those fluids showing a normal cell count and a positive Noguchi globulin reaction the indication was usually faint. In only one instance was there an increased cell content with a negative Noguchi, and this fluid was from a child with brain abscess, two days later the fluid showing changes characteristic of a purulent meningitis. I have observed no selective action in either the Noguchi or Nonne tests in showing the presence of globulin in pathologic cerebrospinal fluids. The occurrence and intensity of the reaction has seemed rather to depend on the amount of globulin present. In advanced conditions the cell content gives more accurate information concerning the nature of the process.

Granting that the colloidal gold reaction is a test for the presence of protein substances and therefore evidence of pathologic change in the cerebrospinal fluid, as is generally conceded, it is unquestionably more delicate than the other tests here used for comparison. This has been the experience of all observers. Every fluid showing the presence of globulin gave a positive Lange reaction. Of eleven questionable colloidal gold reactions, six were bizarre reductions, accounted for only by errors in technic and not likely to cause confusion, and have been considered negative. Five were from children with hereditary syphilis, and the fluids caused only a slight reduction in the syphilitic zone.

There has been noted a certain parallelism between the reduction of the colloidal gold in the various dilution zones and the amount of globulin in the fluid, as estimated by the intensity of the Noguchi and Nonne reactions. That is, those showing only a trace of globulin or none at all reduce the lower dilutions. Those with a higher content reduce the higher dilutions. Such a crude quantitative estimation, of course, is not at all satisfactory, and the amount of coagulable and noncoagulable nitrogenous bodies should be determined before any conclusions are drawn.

That there may be some specific selective action of a substance in the pathologic fluid, without definite relation to quantity, is very probable, because of the uniform evidence of the existence of a typical "paretic curve," occurring with fluids from patients with general paresis.

The reduction of Fehling's solution by the cerebrospinal fluid is of interest chiefly because of its negative value in reference to diagnosis. The amount of reduction varies in normal fluids and reduction has occurred in tests on all pathologic fluids except those from patients with purulent meningitis and advanced tuberculous meningitis. If the presence of dextrose in the cerebrospinal fluid is to be of any value in diagnosis, its estimation must be quantitative.

The high incidence of a permanganate index of more than 2 leads to the evident conclusion that this value can not be taken as a criterion for normal fluids. Of 110 fluids on which this test was made, forty-three were normal, as indicated by a normal cell count and a negative colloidal gold test. The reduction index of these normal fluids varied between 1.4 and 2.7 with an average of 2. In thirty-six fluids taken from patients with syphilis and acute anterior poliomyelitis, showing slight pathologic change, the variation was from 1.4 to 2.9, with an average of 2.4. In more marked meningitic processes the average is found to be definitely higher. In any condition, though, the individual variations are so great that no significance can be placed on a slightly increased permanganate index. Moreover, there is noted no definitely increased index in the early stages of the more severe meningeal inflammation when the test might be of clinical value, the high index occurring only in advanced conditions, in which the nature and cause of the changes are evident.

The reduction of potassium permanganate depends on two factors, namely, the dextrose and nitrogenous bodies. Even in normal fluids the amount of sugar is variable, and this may be true of the nitrogenous bodies. This may explain the wide limits of variation in the reduction index. With a slight increase of protein substance the dextrose may be normal or slightly reduced, hence the lack of uniformity in the indexes of fluids showing little pathologic change. It is only those

TABLE 1.—SYPHILIS

No.	Name	Cell Count	Globulin		Fehling's	Permanganate Index	Lange	Wassermann Reaction	Remarks
			Noguchi	Nonne					
3	E. B.	6	0	0	++	1.4	± 2 3 3 1± 0 0 0 0	++++	Six months later
50	E. B.	30	±	0	+	2.5	2 2 3 3 2± 0 0 0 0	++++	
10	G. McD.	5	±	0	++	2.1	± 2 4 4 4 3± 0 0 0	+++	
18	E. B.	25	+	0	++	2.9	1 2 3 4 1± 1 1 0 0	++	
28	G. D.	1	0	0	+	2.3	± 2 1 1 1±± 0 0 0	++++	Seven months later
62	G. D.	4	0	0	++	2.7	3 3 3 3 2± 0 0 0 0	+	
29	C. S.	6	0	0	+	2.6	3 3 3 2 2 1 0 0 0 0	++++	
36	E. G.	1	0	0	+	2.5	0± 2 2± 0 0 0 0 0	0	
52	I. W.	45	++	+	+	2.4	5 4 5 5 3 3 2± 0 0	++++	
57	I. W.	40	+	+	+	2.3	5 5 5 4 4 3 1 0 0 0	—	One week later
60	P. B.	5	0	0	++	2.9	4 4 4 4 3 2± 0 0 0	0	
61	A. C.	1—	0	0	+	2.5	4 5 5 4 4 3 1± 0 0	0	
64	H. H.	19	+	0	+	2.7	5 5 5 5 4± 0 0 0 0	++++	
66	M. G.	3	0	0	+	2.1	± 1 2 2± 0 0 0 0 0	0	
76	W. N.	5	+	0	++	2.3	2 3 3 3 3 2± 0 0 0	0	
80	R. S.	8	+	0	++	2.3	3 3 3 3 0 0 0 0 0 0	—	

81	B. H.	48	++	+	+	2.5	4 5 5 5 5 5 5 ± 0	++++	Adult G. P.
82	A. W.	16	+	0	+	2.2	± 1 2 3 3 2 0 0 0 0	0	
87	H. W.	23	+	0	+	2.6	3 4 4 4 3 2 ± 0 0 0	++++	
91	A. W.	234	+	0	++	...	4 5 5 4 3 3 3 1 0 0	++++	
94	A. W.	96	±	0	++	2.1	5 5 5 5 4 3 2 0 0 0	—	Intervals of 1 week. Intraspinal treatment, mercurialized serum
101	A. W.	6	0	0	++	2.3	5 5 5 5 4 2 2 0 0 0	++	
92	G. K.	6	0	0	++	1.9	2 3 3 3 1 0 0 0 0 0	0	
95	W. L. G.	22	+	0	++	1.8	0 0 1 2 2 0 0 4 0 4	++	
96	Z. R.	7	0	0	++	2.1	1 2 3 3 1 0 0 0 0 0	0	
97	T. A.	5	+	0	++	1.6	1 1 1 2 3 3 3 0 0 0	0	
98	J. H	1—	0	0	++	2.8	1 2 3 3 2 1 0 0 0 0	0	
102	J. L.	40	++	++	++	2.5	0 5 5 4 4 3 2 0 0 0	++++	
110	H. N.	6	0	0	++	1.8	0 1 2 2 1 0 0 0 0 0	0	
111	N. F.	2	0	0	++	2.7	0 0 0 2 3 3 3 0 0 0	—	
114	C. S.	6	0	0	++	2.3	1 1 2 2 1 0 0 0 0 0	0	
16*	A. P.	1—	0	0	++	1.6	0 0 0 0 0 0 0 0 0 0	0	
17*	L. P.	2	0	0	++	1.6	0 0 0 0 0 0 0 0 0 0	0	
25*	R. M.	2	0	0	+	...	0 0 1 1 0 0 0 0 0 0	0	
71*	L. McG.	4	0	0	++	2.0	0 0 0 0 0 0 0 0 0 0	0	
77*	A. B.	3	0	0	++	2.3	0 0 0 0 0 0 0 0 0 0	0	

* Syphilis, hereditary, latent.

fluids showing a large increase of protein which give a definitely increased permanganate index.

The discussion of the Wassermann reaction on the cerebrospinal fluid has been reserved for consideration in comparison with the other findings in the fluids from cases of hereditary syphilis. In all, thirty-six fluids were examined from thirty-one patients with hereditary syphilis, in all of which the Wassermann reaction on the blood was positive. The colloidal gold showed varying degrees of reduction with the majority of these fluids, and this occurred in the syphilitic zone in every instance but three (Nos. 95, 97, 111).[15] In five of the reactions (Nos. 28, 36, 66, 110,.114) only slight reduction took place, but these have been considered positive in the light of the changes occurring in the syphilitic zone; one of these (No. 28) gave a positive Wassermann reaction. This emphasis is given to the colloidal gold test because of its evident superiority over other tests as an index of central nervous system involvement in hereditary syphilis. Next in value are the Wassermann reaction and the presence of globulin, which are about equal in incidence, though not parallel. The Wassermann reaction, of course, is unique, in that, when positive, it establishes a definite diagnosis. The Lange reaction was positive in every fluid showing other evidence of pathologic change, and in many cases it was the only evidence.

The superior delicacy of the Noguchi test over the Nonne test for globulin was demonstrated in syphilitic fluids as in no other condition, for we are here dealing with small quantities of globulin in most cases.

Pleocytosis occurred only in those children showing more marked evidence of syphilis of the central nervous system both in the clinical and laboratory findings. It is of interest to note that in this series pleocytosis, globulin content, and the intensity of the colloidal gold reaction were parallel.

The clinical evidence of syphilitic involvement of the central nervous system was in direct proportion to the pathologic findings in the cerebrospinal fluid. This was particularly true of the intensity of the colloidal gold reaction. Practically all of the fluids giving a positive Lange were from children showing some degree of mental impairment. Several fluids giving typical paretic curves were from children with marked dementia.[16] The five normal fluids were from children whose only evidence of syphilis was a positive Wassermann reaction on the blood and who were apparently normal in every way.

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15. The changes in No. 95 were apparently due to some technical error. No. 97 had miliary tuberculosis, with some possibility of meningitis; unfortunately there was no opportunity for a second examination. The changes in No. 111 alone cause doubt as to the selective action of syphilitic fluids.

16. G. McD. (No. 10), apparently normal when this examination was made, showed mental deterioration while under observation.

TABLE 2.—TUBERCULOUS MENINGITIS

No.	Name	Cell Count	Globulin		Fehling's	Permanganate Index	Lange	Wassermann Reaction	Remarks
			Noguchi	Nonne					
4	F. C.	160	++	++	±	4.1	±± 1 2 4 4 2± 0 0	0	
6	R. C. H.	4	0	0	++	2.7	± 1 2 2 2±± 0 0 0	—	
8	E. G.	140	++	++	0	4.0	±± 1 3 3 2± 0 0 0	—	
9	A. W.	384	++	++	0	3.7	±±± 2 5 5 5 1 0 0	0	
12	A. B. H.	†	++	++	+	4.0	0 0 0 0 0 3 3 3 2 0	—	
13	H. H.	254	++	++	0	4.1	0 0 0± 4 5 5 2 0 0	—	
15	I. H.	160	++++	++	0	3.4	0 0 1 3 4 4 4 4 2 0	0	
19	W. J. McC.	57	+++	++	0	3.3	± 1 2 4 4 4± 0 0 0	—	
27	F. S.	57	+	+	0	2.4	± 2 4 4 2 2± 0 0 0	—	
30	B. W.	10	0	0	+	2.4	0 2 3 5 5 3 0 0 0 0	—	
53	A. O.	130	++	+	0	3.5	0 0 0 2 3 3 2 0 0 0	..	Later
56	A. O.	135	++	+	0	3.6	0 0 1 3 4 4 3 0 0 0	..	
69	E. K. *.....	16	+	+	+	1.4	0 0± 5 5 3± 0 0 0	—	
89	J. F.	263	+++	++	±	3.1	0 0 0 3 4 4 4 0 0 0	—	
100	B. B.	171	+++	++	+	2.9	1 1 1 4 4 4 4 1 0 0	..	Later specimens
105	B. B.	315	+++	++	±	2.8	2 2 2 2 4 4 4 1 0 0	—	
109	B. B.	340	+	+	0	...	0 1 2 3 3 3 3 3 0 0	—	

* In this case the diagnosis may be questioned, as further observation was prevented by the child's removal from the hospital.
† Cell count not made.

Only three fluids in this series were from young infants (Nos. 60, 82, 98) with acute manifestations of infantile syphilis, and all gave a positive Lange, although the spinal fluid Wassermann reaction was negative. This fact merely points to the possibility of central nervous system involvement, and it would hardly be justifiable to establish a diagnosis of hereditary syphilis, without the Wassermann reaction on the blood, as Grulee and Moody[17] have concluded.

In fluids from fifteen patients with tuberculous meningitis precipitation of the colloidal gold occurred in every instance, the maximum color change occurring in the dilutions 1 to 80, 1 to 160 and 1 to 320 in most cases. Fourteen of the fifteen patients had at the time of the fluid examination, or developed later, typical clinical manifestations of tuberculous meningitis. The diagnosis was confirmed by the demonstration of tubercle bacilli in the cerebrospinal fluid in fourteen cases and by necropsy in ten of them. In most of the cases the diagnosis was fairly conclusive from the clinical signs and the cell and globulin content of the fluid at the first examination. Reduction of Fehling's solution occurred only in the early stages of the disease.

Three of these patients were seen at the very onset (Nos. 6, 30, 69). The cell counts were low and globulin was present in only one. Permanganate indexes were slightly increased in two and low in one. All three fluids caused a maximum reduction of the colloidal gold solution in the same dilutions as found for the rest of the series.

Further observations on early meningeal processes would be valuable, as these few observations suggest a typical zone reaction for tuberculous meningitis, which may be an aid to early diagnosis.

Seven fluids from cases of purulent meningitis gave the typical findings of this condition, namely, a high cell count and globulin content, and the causative organism was found in all but one. The permanganate indexes were all high and Fehling's solution was not reduced. In general the colloidal gold was reduced by the higher dilutions of the fluid, but the intensity of the reaction or the zone affected was not constant. Nos. 11 and 42 are included here because they were obtained shortly before the development of the typical meningitic changes in the fluid. It will be noted that No. 11 caused a reduction of the colloidal gold in the dilutions 1 to 80, 1 to 160, and 1 to 320, the zone suggestive of a tuberculous condition. Certainly it was indicative of a beginning meningeal process and this was borne out by the later developments.

Six fluids from four patients with acute anterior poliomyelitis were examined. Four of these, one from each patient, at the first examina-

17. Grulee and Moody: Jour. Am. Med. Assn., 1913, lxi, 13; Am. Jour. Dis. Child., 1915, ix, 17.

TABLE 3.—PURULENT MENINGITIS

No.	Name	Cell Count	Globulin		Fehling's	Permanganate Index	Lange	Wassermann Reaction	Remarks
			Noguchi	Nonne					
1	F. H.	1,400	++	++	0	4.2	1 1 3 4 3 3 3 2 2 0	—	Streptococcus
2	S. M.	Pus	+++	+++	0	7.6	0 0 ± ± ± 1 2 4 5 5	—	Meningococcus
11	W. B.	14	0	0	+	2.6	0 ± ± 5 5 5 1 ± 0 0	0	Abscess of brain; later, meningitis
14	W. B.	8,000+	+++	++	0	6.3	0 0 ± 1 2 4 5 5 5 ±	—	Staphylococcus
42	E. A.	3	0	0	+	2.5	0 ± ± ± 0 0 0 0 0 0	—	Mastoiditis
46	E. A.	6,000	++++	+++	0	6.1	1 2 0 0 0 0 3 4 4 4	—	Later fluid, meningitis staphylococcus
51	T. H. B.	Pus	++	++	0	4.2	0 0 1 3 4 5 4 3 3 3	—	Cause not determined
55	L. G.	6,000	+++	+++	0	4.3	0 0 0 2 2 3 3 4 4 4	—	Pneumococcus
107	G. W.	3,000	+++	++	0	3.7	0 0 0 1 1 3 3 3 3 3	—	Meningococcus

TABLE 4.—ACUTE ANTERIOR POLIOMYELITIS

No.	Name	Cell Count	Globulin		Fehling's	Permanganate Index	Lange	Wassermann Reaction	Remarks
			Noguchi	Nonne					
44	H. F.	4	0	0	+	2.7	2 2 4 3 2 1 0 0 0 0	0	One week later
47	H. F.	4	0	0	+	2.1	1 1 1 ± 0 0 0 0 0 0	—	
68	A. I.	25	+	0	++	2.6	2 2 3 4 4 4 4 1 0 0	—	
70	P. D.	9	+	0	++	2.0	0 ± 3 4 2 0 0 0 0 0	0	
79	S. W.	16	+	0	++	2.9	3 3 3 3 ± 0 0 0 0 0	0	One week later
85	S. W.	6	0	0	++	2.2	0 0 0 0 0 0 0 0 0 0	—	

TABLE 5.—Miscellaneous Pathologic Fluids

No.	Name	Cell Count	Globulin		Fehling's	Permanganate Index	Lange	Wassermann Reaction	Remarks
			Noguchi	Nonne					
58	H. F.	16	++++	+++	0	9.7	0 0 0 0 ± 1 2 4 4 5	—	Golden yellow color
59	H. F.	42	++	0	±	2.8	4 4 3 2 2 0 0 0 0 0	0	Ventricle fluid clear, colorless same day
73	H. F.	3	+	0	+	2.4	2 3 3 3 ± 0 0 0 0 0	—	Two weeks later clear, colorless lumbar puncture fluid
72	C. M.	2	±	0	++	2.3	1 2 4 4 2 0 0 0 0 0	0	Mongolian idiocy
112	R. C.	686	+	+	++	1.8	1 1 2 2 2 1 0 0 0 0 0	0	
115A	R. C.	330	+	0	....	...	1 1 2 2 2 2 0 0 0 0 0	—	Encephalitis; second and third fluids eight and ten days later
115B	R. C.	310	+	+	++	...	1 2 2 3 3 1 0 0 0 0	—	
90	C. F.	6	0	0	++	2.7	0 0 1 1 0 0 0 0 0 0	0	
93	C. F.	1	0	0	++	...	± 1 2 2 2 2 0 0 0 0	—	Hydrocephalus, brain tumor?
108	C. F.	3	0	0	++	...	1 2 2 2 1 0 0 0 0 0	—	
99	J. H.	2	0	0	++	...	± 2 3 4 4 4 1 ± 0 0	—	Mastoiditis; abscess of brain? Septicemia; no necropsy
117	J. H.	6	....	..	++	2.2	1 2 3 3 3 0 0 0 0 0	—	

tion caused a reduction of the colloidal gold in the so-called syphilitic zone. Two of these showed pleocytosis and three gave positive globulin tests. In two cases (Nos. 47 and 85) fluids were examined after acute symptoms had subsided. In one, slight reduction took place in the lower dilutions, but the other was quite negative. Globulin was not present at the second examination. Wassermann tests made on the blood and cerebrospinal fluid of three of the four patients were negative. This occurrence of an early transitory reaction in the syphilitic zone in the acute stage of anterior poliomyelitis suggests an important aid in the diagnosis of this disease.

Table 5 is a group of fluids which gave evidence of pathologic change by one or more tests. The color changes were in this group almost entirely in the lower dilutions. No. 58 contained a large amount of globulin and albumin and had a golden yellow color. The ventricular fluid (No. 59) from the same patient was clear and colorless. The child recovered and the nature of the meningeal process was not definitely ascertained, although the clinical condition was suggestive of anterior poliomyelitis.

Fluids from R. C. (Nos. 112 and 115 A and B) were remarkable for the high cell count occurring with a small amount of globulin. In the absence of other definite findings, the condition was thought to be one of encephalitis. In the patient C. F. (Nos. 90, 93, 108) necropsy revealed no cortical or meningeal process which would account for the change in the cerebrospinal fluid, though hydrocephalus was definite.

It will be noted that a number of conditions giving obscure fluid changes all reduced the colloidal gold in the syphilitic zone; in some instances this was the only pathologic finding. The blood in these cases gave negative Wassermann reactions, and therefore they may be considered nonsyphilitic. This gives further support to the view mentioned above, that the term "syphilitic zone" is misleading and inaccurate.

In Table 6 are recorded the results of the examination of a number of clinical conditions in which the spinal fluid findings are quite normal.

Cases with meningismus showed no pleocytosis except in one instance (No. 106). All reduced Fehling's solution. The permanganate indexes were low in general, but were too variable to be significant.

It is noteworthy that fluids from epileptics and from nonsyphilitic mental defectives gave no evidence of any pathologic change by any of these tests. Fluids from patients with chorea gave normal findings, including negative Lange tests. In view of the fact that a large number of conditions gave positive Lange tests with no other pathologic findings, and that many of these latter proved to be the result of meningeal inflammation, it seems conclusive that these conditions

TABLE 6.—MISCELLANEOUS

No.	Name	Cell Count	Globulin		Fehling's	Permanganate Index	Lange	Wassermann Reaction	Remarks
			Noguchi	Nonne					
5	L. G.	5	0	0	++	2.0	0±++ 0 0 0 0 0 0	—	Lobar pneumonia
26	E. G.	8	0	0	++	...	0 0 0 0 0 0 0 0 0 0	—	Lobar pneumonia, meningismus
74	D. L.	4	0	0	+	1.8	0 0 0 0 0 0 0 0 0 0	—	Lobar pneumonia, meningismus
84	D. P.	4	0	0	+	2.1	0 0 0 0 0 0 0 0 0 0	—	Bronchopneumonia, meningismus
106	M. McD.	43	0	0	++	1.6	1 2 0 0 0 0 0 0 0 0	0	Otitis media, meningismus
116	S. L.	1	0	0	++	2.0	1 1 0 0 0 0 0 0 0 0	—	Pyelitis, meningismus
118	E. S.	1—	0	0	++	2.4	0 0 1 0 0 0 0 0 0 0	—	Lobar pneumonia, meningismus
35	J. L.	4	0	0	++	1.9	0±± 0 0 0 0 0 0 0	—	Chorea
40	H. P.	10	0	0	++	2.0	0±± 0 0 0 0 0 0 0	—	Chorea
104	R. R.	5	0	0	++	1.9	0 1 2 0 0 0 0 0 0 0	—	Chorea
37	P. W.	2	0	0	++	2.0	0 0 0 0 0 0 0 0 0 0	—	Mental deficiency
48	E. B.	3	0	0	++	2.1	0 0 0 0 0 0 0 0 0 0	—	Mental deficiency
49	E. B.	2	0	0	+	2.2	0 0±± 0 0 0 0 0 0	—	Mental deficiency
67	W. B.	5	0	0	+	2.7	0 0 0 0 0 0 0 0 0 0	0	Mental deficiency
75	G. G.	5	0	0	+	2.3	0 0 0 0 0 0 0 0 0 0	0	Mental deficiency
86	M. W.	2	0	0	++	2.2	0 0 0 0 0 0 0 0 0 0	0	Mental deficiency
39	J. B.	1	0	0	+	2.2	0±++ 0 0 0 0 0 0	0	Epilepsy
65	C. S.	2	0	0	+	2.5	0 0 0 0 0 0 0 0 0 0	0	Epilepsy

83	A. P.	6	0	0	++	2.2	0 0 0 0 0 0 0 0 0 0	0	Epilepsy
88	A. B.	2	0	0	++	1.9	0 0 0 0 0 0 0 0 0 0	0	Epilepsy
103	A. D.	4	0	0	++	1.8	0 0 0 0 0 0 0 0 2 0	0	Epilepsy
113	L. M.	5	0	0	++	1.4	1 1 0 0 0 0 0 0 0 0	0	Epilepsy
20	C. W.	3	0	0	++	2.3	0 0 0 0 0 0 0 0 0 0	—	Tuberculous bronchial glands
21	H. S.	3	0	0	++	2.2	0 0 0 0 0 0 0 0 0 0	—	Pulmonary tuberculosis
22	C. H.	2	0	0	++	1.8	0 0 0 0 0 0 0 0 0 0	—	Pulmonary tuberculosis
23	R. P.	6	0	0	++	2.5	0 0 0 0 0 0 0 0 0 0	—	Tuberculous bronchial glands
24	C. D.	4	0	0	++	2.4	0 0 0 0 0 0 0 0 0 0	—	Pleurisy, effusion
38	G. S.	3	0	0	++	1.9	±± 0 0 0 0 0 0 0 0	—	Tuberculids
41	K. L.	3	0	0	++	2.3	0 0 0 0 0 0 0 0 0 0	—	Pulmonary tuberculosis
31	M. B.	2	0	0	++	2.0	±±± 0 0 0 0 0 0 0	..	Malaria
32	T. B.	3	0	0	++	1.9	0 0 0 0 0 0 0 0 0 0	..	Malaria
33	C. B.	1—	0	0	++	2.2	0 0 0 0 0 0 0 0 0 0	..	Malaria
7	M. B.	8	0	0	+	2.1	0± 1 2± 0 0 0 0 0	..	Status lymphaticus
34	D. C.	2	0	0	++	1.9	0±±± 0 0 0 0 0 0	..	Nephritis
45	J. H.	4	0	0	+	1.9	0 0 0 0 0 0 0 0 0 0	..	Hydrocephalus
54	H. N.	6	0	0	+	2.2	0 0 0 0 0 0 0 0 0 0	..	Tetanus
43	W. K.	1—	0	0	++	2.1	0 0 0 0 4 0 0 0 0 0	..	Purpura
63	I. W.	10	±	0	+	2.1	0 0 0 0 0 0 0 0 0 0	..	Spastic quadriplegia
78	M. K.	4	0	0	++	2.1	0 0 0 0 1 5 3 1 0 0*	..	Septicemia

* Probably due to some technical error. No meningeal lesion revealed at necropsy.

affecting the nervous system, and having normal cerebrospinal fluids, are not meningeal in origin, neither are the meninges in any way affected.

SUMMARY

1. As an index of pathologic change in the cerebrospinal fluid, the colloidal gold reaction is more delicate than any other test here employed. A positive Lange reaction may be considered sufficient evidence of a pathologic process affecting the cerebrospinal nervous system, though the fluid in question is negative to all other tests. A normal fluid causes no reduction of the colloidal gold.

2. The presence of globulin in the cerebrospinal fluid, as determined by the tests of Noguchi and Nonne, is indicative of an inflammatory process, but is of no specific import. A negative globulin test may occur in a pathologic fluid.

3. The quantitative estimation of organic substances by the reduction of tenth-normal potassium permanganate shows such wide variations in normal fluids and those with slight pathologic change that it has no value as a diagnostic measure.

4. The qualitative presence of dextrose in the cerebrospinal fluid as determined by the reduction of Fehling's solution is of little value in the diagnosis of lesions of the central nervous system.

5. The specific diagnostic import of a given test is dependent on the character of the process causing the change in the fluid examined. Thus the cell content and bacteriologic findings are final in purulent and tuberculous meningitis. In the colloidal gold test the characteristic syphilitic zone reaction in hereditary syphilis is sufficient to establish the actual or potential existence of a syphilitic involvement of the central nervous system. This statement presumes a positive Wassermann reaction on the blood.

6. A number of affections give this same reaction, particularly acute anterior poliomyelitis, and no specific significance can be attached in nonsyphilitic cases.

7. The occurrence of a typical zone reaction in the colloidal gold test on fluids from patients with tuberculous meningitis is probable, and may be of value in diagnosis in the early stages. The occurrence of a transitory reaction in the lower dilutions suggests an aid in the diagnosis of acute anterior poliomyelitis.

SOME EARLY SYMPTOMS SUGGESTING PROTEIN SENSITIZATION IN INFANCY*

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DETROIT

Through the painstaking researches of a great number of workers, we have come into possession of much information concerning the action of foreign protein when injected into animals subcutaneously, intraperitoneally or intravenously. The forms of protein most carefully studied are those of the various serums and the incentive for this study had its origin in the revolutionary discoveries of von Behring, Ehrlich, Wassermann, Abderhalden, Wright, Vaughan and a host of other workers. The study of the protein of the various serums led naturally to the study of the protein of the common food products, and out of this has come a great mass of information concerning the protein of milk, egg, meat and cereals. The leaders in the researches are Besredka, Vaughan, Osborn, Anderson and many others. Out of the tremendous amount of work which has been done in an effort to explain the phenomenon of anaphylaxis there have accumulated many facts which seem to be of such importance that they should be transported from the realm of the laboratory and made to serve the clinician in his daily work.

Two members of our society stand out pre-eminently in their efforts to bring to practical use the findings of the laboratory. Dr. Talbot[1] has shown the causal relation between egg protein and asthma; Dr. Schloss[2] has made clear through his researches that certain forms of infantile eczema are related to protein. It was thought for a long time that protein in order to enter the blood stream or body tissues unaltered must be introduced through the skin (subcutaneously, intraperitoneally, intramuscularly) or intravenously, but researches have been so abundant and conclusive during the past few years as to leave us no longer in doubt that a foreign protein, even when taken by mouth, may escape digestion and some of it be absorbed into the blood stream unaltered. The pioneers in this work were Ganghofer and Langer,[3] Lawatschek,[4]

* Submitted for publication May 23, 1916.
* From the Children's Free Hospital of Detroit.

1. Talbot, F. B.: Boston Med. and Surg. Jour., clxxi, 695.
2. Schloss, O. M.: Am. Jour. Dis. Child., 1912, iii, 341.
3. Ganghofer and Langer: München. med. Wchnschr., 1904, li, 1497.
4. Lawatschek: Prag. Med. Wchnschr., 1914, xxxix, 185.

Ascell,[5] Moro,[6] Rosenau and Anderson[7] and Lust.[8] The latest and most convincing researches have just been published by Schloss and Worthen.[9] These workers have demonstrated beyond a question that absorption of protein occurs through the alimentary tract, particularly in those exhibiting signs of nutritional or gastro-enteric disorders. They state: "In gastro-enteric disorders, the mucous membrane becomes permeable, the degree of permeability being in direct ratio, apparently, to the severity of the disorder." My own researches in support of the proof of the absorption of milk protein into the blood stream unaltered are based on anaphylactic reactions in guinea-pigs.

The technic followed was that advised by Vaughan. Blood was collected from infants and children one hour after a feeding which contained milk protein in the usual quantity fed children of such ages. The blood was collected in citrate solution and taken to the laboratory and from 3 to 5 c.c. were injected intraperitoneally into normal guinea-pigs weighing about 250 gm. After suitable time had elapsed (at least 11 days), an injection of 5 c.c. of milk was also made intraperitoneally.

Blood was taken from normal children as well as from those with eczema, malnutrition and acute infections. The work, though still incompleted, confirms the work just published by Schloss and Worthen. Patients with eczema and malnutrition show undoubted permeability of the alimentary tract by positive anaphylaxis tests in guinea-pigs.

Just what happens when the foreign protein is absorbed unaltered into the blood stream has been the subject of numerous researches and much discussion without unanimity, but all are agreed that the individual absorbing such protein behaves differently under certain conditions than an individual who has not received this unaltered protein into its body tissue. This change in behavior toward the foreign protein by the individual is characterized as sensitization, or allergy.

The symptoms caused by the action of body tissue and fluids on this foreign protein is of great interest, for it varies from the mildest disturbance to an explosion of such severity as to cause sudden death. A condition fraught with such far reaching consequences should command our best thought. It is therefore my purpose to attempt to collect some of the earliest signs and symptoms which are evident in the individual thus sensitized. In attempting to determine these symptoms I have studied the symptomatology of a large number of authentic sensitization cases reported in literature. I have also made extremely

5. Ascoll: München Med. Wchnschr., 1902, xlix, 398.
6. Moro, E.: München. Med. Wchnschr., 1906, liii, 214.
7. Rosenau and Anderson: Bull. Hyg. Lab., U.S.P.H.S., 1908, No. 45.
8. Lust: Jahrb. f. Kinderh., 1913, lxxvii, 244.
9. Schloss and Worthen: Am. Jour. Dis. Child., 1911, ii, 342.

careful observations continuing from the time of birth on a considerable number of infants, who have later shown unmistakable signs of sensitization. Also, through the intelligent cooperation of mothers, I have collected a great deal of material concerning the early symptoms of protein sensitization.

A study of the symptomatology of acute anaphylaxis lays for us the groundwork of our suggested early symptomatology of "suppressed anaphylaxis." It might be well to get the picture of anaphylaxis both in guinea-pig and in man as described by Vaughan:[10]

> When a sensitized guinea-pig receives a reinjection of the same protein to which it has been sensitized after a proper interval of time, certain characteristic and practically invariable symptoms develop in three stages. The first stage is that of peripheral irritation. The animal is excited and evidently itches intensely, as is shown by its attempts to scratch every part of its body that can be reached with its feet. The second stage is one of partial paralysis. The animal lies upon its side or belly, with rapid, shallow, difficult breathing. It is disinclined to move, and when urged to do so shows more or less incoordination of movement, and muscular weakness, with partial paralysis, especially observable in the posterior extremities, which it drags. Rarely the animal dies in this stage. The third, or convulsive stage, begins with throwing the head back at short intervals. The convulsions become general, more frequent and violent, and the animal, having reached this stage, usually dies in a convulsion or immediately following one. Expulsion of urine and feces is frequent in the convulsive stage. Recovery after reaching the convulsive stage is exceedingly rare. When this stage is not reached, recovery usually occurs, and is so prompt and complete that after a few hours, or at most by the next day, the animal cannot be distinguished from its perfectly healthy fellows.
>
> When the hemologous protein is injected into a man sensitized by disease or by previous treatments, symptoms develop promptly, often within a few minutes, usually within a few hours. The stage of peripheral irritation is characterized by the sudden appearance of a rash. The rashes that occur most promptly are urticarial or erythematous. The lips and tongue seem swollen, and often the backs of the hands are swollen. The individual becomes apprehensive, says that he cannot breathe, and falls into a state of more or less marked collapse. In extreme instances there is retching, and occasionally vomiting. The second stage, that of great muscular weakness, continues for a variable time and usually rapidly passes away. In rare instances speedy death results.

It will be seen that the symptoms of acute anaphylaxis in both animal and man may be divided into three groups: those relating to (1) the skin, those relating to (2) the upper and lower respiratory tract, and those relating to (3) the digestive system. The condition the symptoms of which we are attempting to give does not derive its impetus from a large quantity of foreign protein suddenly injected into the body tissue, as takes place in the production of acute anaphylaxis, but rather from the absorption of very small quantities every three or four hours, dependent on the interval of feeding. Naturally this slow and oft-repeated method of receiving the protein removes

10. Vaughan: Protein Split Products in Relation to Immunity and Disease, 1913, p. 245.

from the symptomatology the explosive character of the onset, but nevertheless the essential element, namely, the introduction of a foreign protein into the body tissues, should cause essentially the same symptoms, although such milder in form. Particularly is this true if we believe with Vaughan that the symptoms characterizing both acute and suppressed anaphylaxis are due to one and the same cause and differ only in intensity of reaction. Vaughan maintains that in the process of digestion of the protein parenterally the poisonous portion of the protein molecule is set free within the body tissues, and there being no well established protective mechanism, the symptoms of acute or suppressed anaphylaxis take place, dependent upon the quantity and the rapidity with which the poison is set free. Vaughan further states that daily injections of a protein tend to suppress the explosive character of anaphylaxis. This would be analogous to an infant who, being fed daily on milk, absorbed a small quantity of it into the blood stream, unaltered by reason of the permeability of the intestine.

When sufficient quantity of protein is absorbed unaltered, then sensitization takes place and later reaction occurs, not in the explosive character of acute anaphylaxis, but rather in the form of the symptoms of suppressed anaphylaxis; the early evidences of which divide themselves into five definite groups: (1) those relating to the skin; (2) those having to do with upper respiratory tract; (3) those involving the lower respiratory tract; (4) those connected with the digestive organs, and (5) those referred to the nervous mechanism. In addition to this group of symptoms, there is the important condition of family predisposition toward one or another form of protein. In a large percentage of cases under my personal observation it has been possible to learn of some form of sensitization in father, mother or grand parents. It usually shows as hay fever, rose colds, asthma, or distinct reaction to one or another form of food proteins, either egg, bean, oatmeal, milk, beef, fish. It is therefore of very great importance in our study of each case to determine whether or not we have to deal with an offspring whose parents have exhibited definite signs of sensitization.

Let us now consider the symptoms arranged according to the groupings just named. Perhaps the earliest manifestations of sensitization appear in the form of the various lesions of the skin. These may differ greatly in form and intensity. There may be the mildest erythema, either localized or general, or it may take the form of blotchy areas, often of very intense color. There may be urticaria, which may consist of a single wheal or be of the giant type or any degree between these forms. Usually the earliest forms are single urticarial wheals and are often considered by the mother the result of insect bites. There may be rashes, which are usually of the miliary type, and are found particularly about the neck and chest. This form is often thought to

be due to dressing the infant too warmly. In addition to these forms, there may be a mere roughening of the skin, without exposure, similar to chapping.

The whole group of skin lesions due to sensitizations have usually been classified as intestinal rashes. Empirically, they have been associated with food disturbances, but just how they have been brought about has been an open question. Indeed, even with our advanced knowledge, it is difficult to explain the mechanism.

The next common phenomena of sensitization are those connected with the upper air passages. They manifest themselves in diverse ways. There may be symptoms which originate from vasomotor disturbances in the mucosa of the upper air tract. These exhibit themselves in (*a*) sneezing, (*b*) snuffles, and (*c*) rubbing the nose.

Sneezing is often a persistent symptom, until the mother is thoroughly alarmed, believing that the baby is catching a cold. This, coupled with snuffles, which may be so severe that the baby may be forced to breathe through its mouth, constitutes what has been aptly called by mothers a "dry cold." Infants who have been subject to many colds, yet never show a discharge or any other pathologic lesion other than perhaps a rather turgid nasal mucosa, are, in most cases, manifesting one of the common early symptoms of protein sensitization. Rubbing the nose is quite a familiar activity of certain infants and compares with that symptom noted commonly in animals as one of the early accompaniments of anaphylaxis.

The symptoms relating to the respiratory tract are usually of much later occurrence than those of the upper air tract. They are (*a*) wheezing, (*b*) periods of increased respiration, and (*c*) cough.

Wheezing is a very outstanding symptoms and one which can be readily detected. The expressions that mothers often use are that the child "breathes heavily" or that it "wheezes in its chest." This, in some of my cases, has been a very early symptom and precedes the true asthmatic attack by months. When one listens to one of these wheezing chests he is disappointed in finding so few variations from normal. The changes consist chiefly in increased breath sounds with a prolonging of the expiratory portion. The symptom of increased respiration is at first without dyspnea, but later with some dyspnea. These appear quite a time before the true asthmatic attack occurs. A cough occurs in some children, simulating that of mothers' croup, for which there is no adequate pathologic explanation. The cough is often very persistent, but usually is of short duration and disappears as suddenly as it comes on.

The symptoms relating to the digestive system often appear in the presensitization period and consist of an acute digestive disturbance. This is followed later by occasional vomiting attacks, in which an entire

feeding may be ejected suddenly without any apparent cause. This vomiting is often accompanied by one or two urticarial wheals or by some one of the numerous skin manifestations.

The symptoms arising from some disturbance of the nervous system include the conditions generally described under the words irritable, restlessness, fretful and sleepless. Peripheral nerve irritability is very marked. It is most exasperating to watch an animal entering on an anaphylactic shock as it attempts to respond to the call of peripheral nerve endings. Something akin to this no doubt is experienced by an infant and produces for the time being periods of irritability, restlessness, and fretfulness. Sleeplessness is a rather frequent accompaniment of sensitization. Among several of my cases this was the outstanding characteristic and was the condition for the alleviation of which I was consulted.

General Characteristic of Symptoms: All of the above symptoms come and go with great rapidity. Not all of them occur together; often but one of them occurs and quickly disappears. Later on in the same child there is a different manifestation. As the sensitization becomes more marked, the symptoms increase in severity as well as in variety. If the food protein is constantly increased, as is usual in bottle-fed infants, the manifestations of sensitization appear more frequently, remain longer and are more intense; thus many transient erythemas and fine rashes become displaced by the more permanent eczema, which appears first only in a few spots, as on the cheeks, over the fontanel, and behind the ears. If protein is persistently increased, the eczema gradually spreads until the entire body surface may become involved.

In like manner the respiratory symptoms become more prominent. The wheezing is more marked, the breathing more labored and eventually the extreme manifestation appears in the form of an attack of asthma. It rather frequently happens that the extremes of both the skin and the respiratory manifestations occur in one and the same patient, in which case we have a child with severe eczema suffering from frequent attacks of asthma. The other symptom groups tend to become more manifest and the finished product of protein sensitization presents a distressing picture. Fortunately all the symptom groups do not tend to appear in the same child. Certain children appear to be more susceptible to the skin manifestations, while others will show only the upper air tract symptoms, while in others the respiratory symptoms predominate.

I have mentioned only those symptoms which occur early in the period of sensitization. Some of these symptoms persist throughout the lifetime of the individual. Others disappear in the early years of life.

The process by which one becomes immune is little understood, although it has been possible to produce immunity, as demonstrated by both Talbot and Schloss. The relation of protein sensitization to various nutritional disturbances has been referred to by Schloss and Worthen. In their summary they state that their "results demonstrate the possibility that certain nutritional disorders in artificially fed infants may be due to the biologic character of the food." This line of research is well worth continuing, since it has already been shown by Vaughan that marasmus is one of the terminal symptoms of suppressed anaphylaxis in rabbits which have received daily injections of a foreign protein.

I am well aware that many of the symptoms named are symptoms of other very common diseases, and it is not my desire to claim that they occur only as symptoms of protein sensitization; but it is my observation that when the group of symptoms as outlined occurs and reoccurs in an infant early in its existence, one should be on guard and should carefully watch for further developments.

Various tests may assist in diagnosis (*a*) blood examination for eosinophilia, (*b*) cutaneous skin reactions, (*c*) precipitin tests on urine, and (*d*) anaphylactic reactions. It is extremely important that this condition be recognized early, and when so recognized it need not go on to its extreme manifestation in the forms of eczema, asthma, malnutrition and, I have no doubt, many other nutritional disorders whose relation to protein sensitization have not yet been proved.

SUMMARY

1. I believe that permeability of the alimentary tract to unaltered protein in certain infants has been fully demonstrated.

2. The absorption of this unaltered protein produces a group of symptoms, mild at first, and later increasing in intensity, which I believe to be an expression of "suppressed anaphylaxis."

3. By early recognition of such cases, followed by proper food modifications, the symptoms may entirely disappear or be greatly ameliorated.

THE CREATININ AND CREATIN CONTENT OF THE BLOOD OF CHILDREN *

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There are comparatively few data on the creatin-creatinin content of the blood, as it was not until 1914 that a satisfactory method for its determination was devised by Folin.[1] At the same time Folin and Denis[2] reported the results of a number of determinations in adults with different clinical conditions. They found that the blood content of normal adults averaged a little over 1.1 mg. of creatinin per 100 c.c. They were unable to find any specific creatinin retention, but found an increased retention (over 20 mg.) in some cases of nephritis. About the same time Neubauer,[3] in a paper on the use of creatinin as a test of renal function in nephritis, stated that creatinin retention in the blood was very high in some cases of nephritis, reaching 20 mg. per 100 c.c., and that normally it was present in quantities less than 1 mg. per 100 c.c. He gives no other figures.

In two more recent papers Myers and Fine[4] and Myers and Lough[5] report the result of some studies of the creatin-creatinin content of the blood in nephritis. They found, as Folin found, a high retention figure in some cases, but not in all. They noted that all their cases of nephritis with a retention of over 5 mg. of creatinin per 100 c.c. terminated fatally. Of these, there were eleven cases. In all they studied thirty nephritics. In only five patients was the retention under 2 mg. (normal values) and two of these died. From a clinical point of view they consider a case with a creatinin content between 3 and 5 mg. as having an unfavorable prognosis, and those with over 5 mg. as fatal. In a number of normal cases tested they found the creatinin content under 2 mg. per 100 c.c. of blood in almost every case.

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* From the Department of Pediatrics of the Washington University Medical School and St. Louis Children's Hospital.
* Read at the Twenty-Eighth Annual Meeting of the American Pediatric Society, held at Washington, D. C., May 8-10, 1916.

1. Folin: Jour. Biol. Chem., 1914, xvii, 475.
2. Folin and Denis: Jour. Biol. Chem., 1914, xvii, 487.
3. Neubauer: München. med. Wchnschr., 1914, lxi, 857.
4. Myers and Fine: Jour. Biol. Chem., 1915, xx, 391.
5. Myers and Lough: Arch. Int. Med., 1915, xvi, 536.

The creatinin retention in nephritis is apparently but a part of the general retention of nitrogenous substances in the blood, which has been noted by many observers, and there is a definite parallelism between the creatin retention and the retention of the total nonprotein nitrogen, urea and uric acid. There is no evidence at hand leading one to consider it a more delicate index of retention than any of the other nitrogenous substances, and in fact it seems to be more easily excreted.

In the figures obtained by both of these groups of workers the creatin content varied widely and neither paper discusses the creatin figures. If one studies the tables of Folin and Denis it will be noted that the creatin content of the blood averages about 10 mg. per 100 c.c.

Because of the difference in the creatin-creatinin metabolism in adults and children, as measured by their content in the urine, we decided to test the blood of a number of children with different clinical conditions and compare the results with the total nonprotein nitrogen of the blood.

Folin and Denis[6] found that the content of nonprotein nitrogen in the blood of a healthy adult was from 22 to 26 mg. per 100 c.c. Later they published determinations made in a large number of clinical conditions, which showed that there is a definite increase or retention of the nonprotein nitrogen in nephritics with uremia, and that greater variations are found in the blood of hospital patients. Slightly higher values are not necessarily associated with renal disturbance. These findings have been confirmed by a number of observers. There is an increase of from 4 to 6 mg. after a full meal, and usually a slight increase in acute infections. In nephritics the content may vary from normal to ten times normal, the high values being found in actual or impending uremia.

In children the nonprotein nitrogen content does not differ in any marked degree from the adult. Tileston and Comfort[7] made determinations on fifty-one children with a variety of clinical conditions. Normal children gave values of from 20 to 34 mg. per 100 c.c. Only one case, that of a child with acute nephritis, showed a definitely increased value (63 mg. per 100 c.c.), and this later became normal with the disappearance of uremic symptoms. The rest of the observations were made on children with acute and chronic infections, in whom normal values (20 to 32 mg. per 100 c.c.) were found. In normal infants the nonprotein nitrogen content has been found to vary between 23 and 44 mg. per 100 c.c. by Schlutz and Pettibone,[8] whose observations were made on nine infants from ½ hour to 10 days old.

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6. Folin and Denis: Jour. Biol. Chem., 1913, xlv, 29.
7. Tileston and Comfort: Am. Jour. Dis. Child., 1915, x, 278.
8. Schlutz and Pettibone: Am. Jour. Dis. Child., 1915, x, 206.

TABLE 1.—Nitrogen Retention in Children in Scarlet Fever and Various Clinical Conditions

Initials	Sex	Age, Years	Condition	Creatinin, C.c.	Nonprotein Nitrogen, C.c.	Creatin, C.c.
A. C.	♀	2	Normal	1.41	22 0	7.17
C. H.	♀	3	Normal	1.20	26.0	4.70
B. V.	♂	7	Normal	3.44	26.0	2.77
C. C.	♂	9	Normal	2.80	26.0	4.10
T. H.	♂	12	Normal	2.30	33.0	6.40
N. M.	♀	13	Normal	0,78	29.0	4.92
L. K.	♀	14	Normal	2.30	30.0	4.55
E. B.	♂	5	Normal	0.97	25.0	7.16
M. R.	♀	9	Normal	1.92	27.0	2.95
M. R.	♀	8	Normal	0.90	32.0	2.21
M. K.	♀	3	Normal	0.79	32.0	3.41
C. Z.	♂	8	Normal	2.70	31.0	2.60
H. Z.	♂	5	Normal	0.58	28.0	3.92
C. P.	♂	3	Normal	3.24	28.0	3.22
M. R.	♀	12	Normal	1.00	31.0	3.40
R. D.	♀	2	Normal	0.68	25.0	3.54
E. B.	♂	11	Scarlet fever (febrile): Severe	3.44	31.0	3.16
F. S.	♂	5	Mild	1.38	29.0	5.28
A. C.	♂	4	Severe	1.62	22.0	5.83
D. B.	♂	2	Severe	2.38	34.0	1.85
M. M.	♀	8	Mild	1.42	28.0	2.97
I. M.	♀	6	Mild	1.82	27.0	3.23
I. H.	♀	4	Mild	1.08	16.0	....
M. I.	♂	6	Mild	2.79	29.0	2.58
J. W.	♂	11	Mild	1.77	35.0	3.73
A. F.	♂	6	Mild	1.61	32.0	4.11
H. B.	♂	1⅝	Severe	3.82	26.4	4.12
O. B.	♂	3	Severe	2.03	21.5	3.91
A. M.	♀	5	Severe	2.32	29.0	3.14
B. S.	♀	4	Severe	1.91	21.0	2.62
I. F.	♂	4	Severe	3.00	25.0	2.38
L. M.	♀	12	Scarlet fever (afebrile): Early	1.87	19.0	5.67
A F.	♂	2½	Early	1.43	30.0	3.84
M. E.	♀	3	Early	2.38	18.0	3.41
L. O.	♂	10	Early	2.12	19.0	4.06

TABLE 1.—NITROGEN RETENTION IN CHILDREN IN SCARLET FEVER AND VARIOUS CLINICAL CONDITIONS—(*Continued*)

Initials	Sex	Age, Years	Condition	Creatinin, C.c.	Nonprotein Nitrogen, C.c.	Creatin, C.c.
			Scarlet fever (afebrile):			
S. M.	♂	3	Early	2.78	18.5	3.17
W. J.	♂	6	Early	2.20	33.0*	3.68
E. W.	♂	4	Early	2.27	14.5	3.78
C. L.	♂	7	Early	2.36	30.0	2.51
G. N.	♀	8	Early	1.06	25.0	3.94
H. B.	♀	9	Early	1.33	23.0	2.29
			Reexamined (3d week):			
J. W.	♂	11	" "	1.34	32.0	4.51
A. F.	♂	6	" "	1.28	20.0	4.85
M. I.	♂	6	" "	2.80	29.0	5.53
H. B.	♀	9	" "	1.62	22.5	4.63
G. N.	♀	8	" "	1.21	21.7	3.97
I. M.	♀	6	" "	1.44	24.0	4.06
M. M.	♀	8	" "	1.27	22.4	3.44
I. H.	♀	4	" "	0.62	27.0	4.80
C. L.	♂	7	" "	0.94	21.6	3.22
H. C.	♂	5	" "	1.90	22.3	3.41
F. S.	♂	5	" "	1.00	24.5	4.21
			Congenital heart disease:			
M. S.	♀	9	Pulmonary stenosis	0.99	33.0	2.80
F. B.	♂	1	Pulmonary stenosis	0.74	29.0	....
R. R.	♀	8	Chorea	2.50	26.0	4.50
Mc. G.	♂	9	Typhoid conv.	3.22	30.0	4.53
			Nephritis:			
R. C.	♂	3	Acute	1.46	23.0	....
M. D.	♀	3	Chronic diffuse	2.52	42.0	7.20
L. V.	♂	8	Chronic diffuse	2.07	20.0	....
K. P.	♂	1½	Acute (mild)	1.21	36.0	5.28
V. R. 1/17	♀	6	Acute (severe)	0.80	39.0	....
V. R. 1/28	..	..	Severe	1.66	49.0	....
V. R. 3/15	..	..	Severe	1.77	18.0	....
V. R. 4/8	..	..	Severe	0.98	21.7	....
R. K.	♂	11	Tuberculosis, open pulmonary	1.67	23.0	10.00
L. O. N.	♂	13	Tuberculosis, open pulmonary	0.71	32.0	5.00
L. S.	♀	6	Tuberculosis, open pulmonary	1.40	35.0	5.50
M. S.	♀	5	Tuberculosis, open pulmonary	1.78	40.0	3.68
M. H.	♂	14	Anemia, malarial	0.83	49.0	6.74

TABLE 1.—NITROGEN RETENTION IN CHILDREN IN SCARLET FEVER AND VARIOUS CLINICAL CONDITIONS—(*Continued*)

Initials	Sex	Age, Years	Condition	Creatinin, C.c.	Nonprotein Nitrogen, C.c.	Creatin, C.c.
W. P.	♂	11	Anemia, secondary	1.54	25.8	....
M. B.	♀	10	Myocarditis	0.76	24.0	4.78
L. C.	♂	8	Cardiac decompensation	3.20	29.0	2.20
H. S.	♀	9	Chronic bronchitis	1.60	24.0	2.25
M. N.	♀	7	Chronic bronchitis	1.71	40.0	4.53
S. F.	♂	1	Chronic bronchitis	1.49	32.0	4.15
H. K.	♀	2/3	Chronic malnutrition	2.85	20.0	3.00

The methods used in our study were those of Folin and Denis[9] for the nonprotein nitrogen and of Folin[1] for the creatin and creatinin. In the latter test the blood was laked in distilled water before shaking with picric acid, instead of being laked in a saturated solution of picric acid. Five c.c. of blood were used in determining the nonprotein nitrogen (N. P. N.) and 6 c.c. for the creatinin ($Cr._1$) and creatin ($Cr._2$) determinations. All figures are for milligrams in 100 c.c. of blood.

Determinations were made on seventy-five children. Many of these, particularly those with scarlet fever, were tested a number of times. In order to avoid any factor which might result from the ingestion of food, the blood for the tests was taken early in the morning before the children were given their breakfast, and thus about twelve hours after the last meal. The children were placed on a creatin-free diet for the study. In Table 1 the results in seventy-seven tests are tabulated. The cases are grouped into normals; scarlet fever at the time of exanthem, when there was an elevation of temperature; afebrile scarlet fever, in the first week; and a number of examinations made in the third week of convalescence (negative urinary findings). In addition a number of miscellaneous conditions are added.

The creatinin figure for normal children varies between 0.58 and 3.44 mg. per 100 c.c. In ten children the figure was under 2 mg., and in two above. The febrile scarlet fever cases varied between 1.08 and 3.82 mg., but with half above 2 mg. and none under 1. The highest figure in an early afebrile case was 2.78, but in half the cases the content was a little over 2 mg. In convalescence only one case in eleven had a content above 2 mg. Like variations were encountered in the miscellaneous conditions. There was no specific retention in any of our cases, although as a whole the figure for the creatinin content of the

9. Folin and Denis: Jour. Biol. Chem., 1912, xi, 527.

blood in children is somewhat higher than that for the adult. A comparison of the creatinin content with the nonprotein nitrogen is briefly shown in Table 2, in which the cases are grouped according to the amount of each present.

Under 30 mg. of nonprotein nitrogen and 2 mg. of creatinin are considered as corresponding to average normal figures and hence are grouped together. In Group 2 are cases with a figure of from 30 to 35 mg. of nonprotein nitrogen and from 2 to 3 of creatinin per 100 c.c.; Group 3, from 35 to 40 of nonprotein nitrogen and from 3 to 4 of creatinin; Group 4, over 40 mg. of nonprotein nitrogen and 4 of creatinin.

TABLE 2.—Comparison of Creatinin and Nonprotein Nitrogen Content in Various Clinical Conditions

	Group 1		Group 2		Group 3		Group 4	
	Nonprotein Nitrogen	Creatinin	Nonprotein Nitrogen	Creatinin	Nonprotein Nitrogen	Creatinin	Nonprotein Nitrogen	Creatinin
Normal	11	10	5	4	..	2	..	..
Scarlet fever	11	8	4	4	..	3	..	..
Scarlet fever (afebrile)	17	14	4	7	..	..	..	..
Tuberculosis	1	4	..	..	2	..	1	..
Nephritis	2	3	..	3	2	..	2	..

In addition, the nonprotein nitrogen and creatinin were both in Group 2 in two cases each of congenital and of chronic valvular heart disease and in a case of myocarditis. In a child with secondary anemia and in one who had been starved for two days the nonprotein nitrogen was high (over 40), while the creatinin was low. In a typhoid convalescent, in a child with cardiac decompensation and in one with chorea the creatinin figure was in a higher group. As a rule both the nonprotein nitrogen and the creatinin were within the same general limits as have been found for normal adults, and as Tileston found for the nonprotein nitrogen in children, although as a whole the average figures for both are a little higher in children.

We have been able to study but six cases of nephritis. The retention figures in these were not high and but one case was fatal (not uremic). As noted in Table 1 the nonprotein nitrogen was not increased in two cases and the creatinin was normal in three. In one case with a low nonprotein nitrogen figure the creatinin was high and in

two an opposite condition held. As the nephritis in a given case subsides the amount of retention decreases, as illustrated by the case shown in Table 3.

TABLE 3.—Decrease of Nitrogen Retention with Subsidence of Nephritis

Date	Non-protein Nitrogen	Creatinin	Creatin
1/17/16	39	0.80	5.45
1/28/16	49	1.66	4.55
3/15/16	18	1.77	4.61
4/ 8/16	22	0.97	5.15

A number of cases of scarlet fever were followed from the stage of the acute exanthem until desquamation was completed and tests made weekly for five weeks. None of the fourteen cases followed developed a typical postscarlatinal nephritis in the third or fourth week. After the acute febrile period was over, there was usually a slight fall in the nonprotein nitrogen and creatinin, although in the second week a few showed a slight increase. One severely toxic patient, who died in the third week, showed an increasing retention. The kidney in this case showed acute fatty degeneration.

TABLE 4.—Increasing Nitrogen Retention with Progressive Postscarlatinal Nephritis

	Nonprotein Nitrogen	Creatinin
First week	28	1.51
Second week	34	2.38
Third week	47	....

Although as stated there was no discussion of the creatin figures in the earlier papers, a study of Folin's tables shows that in a general way the creatin of the blood of adults averages about 10 mg. per 100 c.c. There is no apparent relationship between the amount of creatin and creatinin. We found much less creatin in the blood of children, rarely over 5 mg. per 100 c.c., and the figure for the total creatin-creatinin was rarely over 6 mg. This is interesting in view of the fact that creatin is found in the normal urine of children and is not present in the urine of adults. We have been unable to find any specific relationship in our figures between the creatinin and creatin, or any relation

between the amount of creatin and the clinical condition. There is no definite relation between the total nonprotein nitrogen and the creatinin-creatin content.

A few experiments were made to observe the influence of certain factors on the nonprotein nitrogen and creatinin content. In one the effect of copious water drinking to flush the kidneys was tried. A fixed diet was given for six days. On the first three days but 200 c.c. of water was allowed, on the fourth and fifth, 2,000 c.c. and on the sixth day 3,000 c.c. Determinations were made on the morning following the last five days. The effect was negligible, as is shown by the figures in Table 5.

TABLE 5.—Effect of Copious Water Drinking on Nitrogen Retention

Water Daily, C.c.	Nonprotein Nitrogen	Creatinin	Creatin
200	28.0	1.18	3.38
200	23.8	2.00	3.24
2,000	25.7	1.41	3.60
2,000	26.0	1.33	3.42
3,000	22.5	1.15	....

Determinations were also made on a child who was being starved for other purposes. A slight increase in the content of all three substances was observed during the period of starvation. An increased creatinin excretion in the urine occurs during starvation.

TABLE 6.—Effect of Starvation on Nitrogen Retention

Day	Diet	Nonprotein Nitrogen	Creatinin	Creatin
1	Regular	31	1.39	4.86
2	Starvation	34	1.67	3.97
3	Starvation	35	1.70	6.70
4	Regular	31	1.36	4.10
5	....	..	....	....
6	Regular	..	1.24	3.56

Several children were placed on a fixed creatin-free diet for six days and analysis of both the urine and blood made daily after the second day. The figures obtained in two cases are given in Table 7.

In the first case both the absolute and relative (percentage relation to total nitrogen) amount of creatinin of the blood varied considerably, while in the second it is quite uniform. In the first case, as in others, there seems to be no definite relationship between the creatin of the blood and of the urine, or between the quantities of total creatin-creatinin.

TABLE 7.—NITROGEN CONTENT OF BLOOD AND URINE ACCOMPANYING CREATIN-FREE DIET

Blood, Mg. N per 100 C.c.			Urine, Total N		
Nonprotein	Creatinin	Creatin	Total Nitrogen Grams	Creatinin Mg.	Creatin Mg.
L. O'N.*					
17.8	0.84	4.60	7.32	541	59
21.9	0.67	3.78	5.82	476	12
22.1	1.90	4.70	5.46	379	82
22.8	1.46	4.57	....	...	...
21.5	2.04	3.52	6.67	542	83
W. P.†					
26.7	1.33	....	3.54	330	95
25.8	1.54	....	3.24	312	123
21.3	1.54	....	3.72	333	270
27.0	1.25	....	3.63	381	206

* Fourth week of mild scarlet fever.
† Secondary anemia.

The second case is given to show the very slight daily fluctuation of creatinin sometimes observed. What mechanism controls the relation between the amount in the blood and the quantity of the urine we were unable to ascertain. The amount of creatin-creatinin to total nonprotein nitrogen in 100 c.c. of blood is much greater than the proportion of creatinin to total nitrogen of the urine.

THE ENERGY METABOLISM OF A CRETIN *

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Studies of the glands of internal secretion have shown that the thyroid gland has a very profound effect on the energy metabolism. An overproduction of the active element of the gland increases the irritability of the nervous apparatus and raises the metabolism, while an underproduction reduces the irritability of the nervous system and lowers the metabolism. The former symptoms are shown clinically in exophthalmic goiter and the latter in myxedema and cretinism.[1]

Magnus-Levy[2] established the fact that in exophthalmic goiter the energy requirements were greatly increased, being from 50 to 70 per cent. above the normal, and that in myxedema and cretinism[3] the heat production might be as low as 45 to 50 per cent. below the normal. Du Bois[4] reported briefly the results of his researches in Professor Lusk's laboratories, in which he studied the diseases of the thyroid gland and obtained similar results to those of Magnus-Levy. Du Bois says:

> In one cretin who was 36 years old, but had the mental and physical development of a child of 8, the total energy requirement was from 18 to 25 per cent. below the normal, but was raised almost to the normal on the third day of treatment with thyroid extract.
>
> The boy, C. G., who was studied in this investigation, entered the children's ward of the Massachusetts General Hospital, Jan. 18, 1915, aged 3 years and 8 months. He was born at full term, and it was necessary to use artificial respiration for ten minutes before he breathed. His parents said he weighed 14 pounds at birth. He was breast fed entirely for one year. During the second year he was given whole milk and crackers, and after that cereals and bread were added to the diet. He was unable to feed himself, could not speak any words, and was unable to sit up alone. His parents thought that he recognized them. The physical examination showed a stupid, well-nourished, fat child, with very little musculature, lying in bed with a blank facial expression. He was phlegmatic and remained quiet most of the time, but when he cried, his voice was hoarse. The hemoglobin was 70 per cent. The skin was pale, sallow, dry, thickened, and wrinkled. The hair was coarse, bristly and dry. The anterior fontanel, though closed, still showed a depression. The tongue was thick, and protruded from the mouth most of the time. The extremities were shorter than normal; the hands square and thick, the skin

* Submitted for publication May 17, 1916.

* From the Nutrition Laboratory of the Carnegie Institution of Washington, and the Children's Medical Department, Massachusetts General Hospital.

1. Lusk: Science of Nutrition, Ed. 2, Philadelphia and London, 1909, p. 268.
2. Magnus-Levy: Berl. klin. Wchnschr., 1895, xxxii, 650.
3. Magnus-Levy: Ztschr. f. klin. Med., 1904, lii, 201.
4. Du Bois: Jour. Am. Med. Assn., 1914, lxiii, 827.

over them being wrinkled. There was a slight umbilical hernia, and there were marked supraclavicular pads of fat. Otherwise the physical examination was normal, except for a systolic murmur heard over the whole precordia. He was the typical picture of a cretin, with the mental development about that of a four to six months old infant. His weight on entrance was 11,800 gm.

His energy metabolism was studied after feeding, in the apparatus furnished by the Nutrition Laboratory of the Carnegie Institution of Washington.[5]

Since he was larger than the infants for which the chamber had been planned, there was very little room to spare after he was in it. This, however, did not seem to bother him during the first observations,

Fig. 1.—Metabolism of cretin, C. G.

on January 19, when two very quiet periods were obtained, and are marked with a star in Table 1 as minimum periods. On January 30, after a course of ten days' treatment with thyroid extract, he had improved very markedly, showed more intelligence, became more active, and showed signs of discomfort in his restricted quarters. He was relatively very active and it was impossible, unfortunately, to get minimum periods for comparison after he was treated.

5. The technic has been previously described by Benedict and Talbot: Carnegie Publication 201, 1914, p. 32.

The lack of data of the metabolism of normal children makes comparisons of the metabolism of C. G. less satisfactory. Table 2, however, is given to show his metabolism compared to two healthy infants, one of which was aged 8½ months, and the other 10 months.

TABLE 1.—ENERGY METABOLISM OF C. G., CRETIN

Date, 1915	Body Weight and Surface	Height, Cm.	Heat Produced per 24 Hours, Calories			Average Pulse Rate	Relative Activity
			Total	Per Kilogram	Per Square Meter Lissauer		
Jan. 19	11.83 Kg.	85	460†	..	.....	94	Quiet
	$10.3\sqrt[3]{w^2} = 0.535$ sq. m.		464	39	867*	95	Quiet
			497	42	929*	95	Very active
			616	52	1,151	116	
Jan. 30	10.78 Kg.	85	672	..	.....	119	Very active
	$10.3\sqrt[3]{w^2} = 0.508$ sq. m.		725	67	1,441	127	Very active

* Minimum periods of heat production, pulse and activity.
† Preliminary period, not used in calculations.

TABLE 2.—COMPARISON OF METABOLISM OF THE CRETIN C. G. WITH THAT OF TWO NORMAL INFANTS

Name	Age	Body Weight Without Clothing	Height, Cm.	Heat Produced per 24 Hours, Calories		
				Total	Per Kg.	Per Sq. M. Body Surface, Lissauer
Normal Infants:						
R. L.	8½ mos.	7.58	71	455	59	1,140
E. G.	10 mos.	9.37	74	480	51	1,046
Creatin, C. G. ..	3 yrs. 8 mos.	11.83	85	479*	40½*	898*

* Average of two quiet periods.

Table 2 is given for comparison because there are no available figures of normal children during the fourth year of life. It is obviously valueless to compare C. G.'s metabolism with that of the adult or with that of Du Bois' 36-year-old cretin. One might speculate as to how the metabolism of C. G. would compare with that of an infant of his own age. In place of that, Table 2 is given as the most available substitute.

The total metabolism for twenty-four hours of these three babies was not very far apart. The comparison of the metabolism per square meter of body surface and per kilogram of body weight is of greater importance since it shows that in both instances the metabolism of the cretin is at least 25 per cent. lower than that of the two infants. Since the cretin was a fat, phlegmatic individual, who did not move much, one would expect that his metabolism would be lower than that of a well-muscled, active baby.[6] It is evident that he was living on a very low plane and that his energy metabolism was considerably lower than what one would expect for a child of his age. These results, while inconclusive, because of the scarcity of material for comparison, are consistent with the findings of Du Bois and others.

6. Talbot: The Energy Metabolism of an Infant with Congenital Absence of the Cerebral Hemispheres, Arch. Pediat., 1915, xxxii, 452.

OBSERVATIONS ON THE TENDENCY OF THE DIPHTHERIA BACILLUS TO LOCALIZE IN THE UPPER RESPIRATORY TRACT

THE IMPORTANCE OF THIS FACT IN ROUTINE CULTURE WORK *

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Because of past experiences in finding that the organisms of diphtheria may be present in the larynx and absent in cultures taken from the nose and throat, or positive in the nose and absent in the throat, and so on, at the suggestion of Dr. Cowie I have made a number of observations with this point in view.

Of the eight cases which I wish to report, the organisms confined themselves to one locality in five cases, which I classify as Group 1; to more than one locality in three cases, which I classify as Group 2.

GROUP 1

CASE 1.—Ione O., aged 25, with marked clinical unitonsillar diphtheria, entered the hospital Feb. 8, 1916. Diphtheria organisms were present in every culture taken from the right tonsil, absent from every culture taken from the left tonsil and pillars, the pharyngeal wall and lateral bands and from the nose. A total of thirty-three cultures, covering a period of twelve days, was taken. Antitoxin, 10,000 units, was administered intravenously, and 10,000 units intramuscularly.

On March 3, 1916, the patient returned, complaining of slight epistaxis, but a nose culture was negative.

CASE 2.—Luella S., aged 21, with marked clinical diphtheria of the lateral bands, entered the hospital Jan. 25, 1916. General cultures taken January 26 and 29 gave positive findings. Special cultures were begun February 1. The organisms were at all times present in cultures taken from the pharyngeal wall and lateral bands, but were not found in cultures taken from the tonsils and pillars or in those from the nose. A total of twenty-two cultures was taken, covering a period of twenty days. Antitoxin was administered, 10,000 units intramuscularly, 10,000 units intravenously.

CASE 3.—Ruth W., aged 21, a diphtheria carrier, entered the contagious hospital Dec. 2, 1915, having suffered with nose bleed two weeks before. General throat culture was negative; nasal culture positive. Nose and throat cultures taken simultaneously showed in each instance organisms in those taken from the nose, but not at any time in those taken from the throat. A total of thirty cultures, covering a period of twenty days, was made. The patient was discharged from the hospital after three negative cultures, the last one being taken Dec. 22, 1915.

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* Submitted for publication April 27, 1916.

* From Department of Pediatrics and Contagious Diseases, University of Michigan, Ann Arbor.

March 18, 1916, she returned to the hospital, again showing positive general throat cultures. Special cultures were again instituted, and it was found that a positive culture was in each instance obtained from the pharyngeal wall and lateral bands, but cultures from the tonsillar fossae and from the nose were negative. (This patient had had adenoid and tonsil operation previous to her first entrance to the hospital.) Total cultures numbering twenty-five were taken, covering a period of fourteen days. The patient is still under observation. The Schick test is negative.

CASE 4.—Ernest D., aged 23, entered Contagious Hospital Feb. 29, 1916, showing mild clinical laryngeal diphtheria. Organisms were present in cultures taken from the larynx, but absent each time in cultures taken from the tonsils and pillars and from the pharyngeal wall and lateral bands and nose. Total cultures numbering twenty-five were taken, covering a period of sixteen days. Antitoxin was administered intravenously, to the amout of 10,000 units.

CASE 5.—Marion Y., aged 20, entered the Contagious Hospital service Jan. 5, 1916, showing laryngeal diphtheria. General culture in this case taken January 1, in the beginning of the illness, was negative. The organisms were present in cultures taken directly from the larynx until January 4. After this, cultures were taken from the tonsils and pillars, the pharyngeal wall, lateral bands and from the nose. They were in every instance negative. Total cultures numbering twenty-eight were taken, covering a period of thirty-one days. Antitoxin was administered, 10,000 units intravenously, 20,000 intramuscularly.

GROUP 2

CASE 6.—John S., aged 2, a diphtheria carrier, entered the Contagious Hospital, Dec. 9, 1915. This patient had harelip and cleft palate, enlarged tonsils and a visible mass of adenoids. A general culture, made Feb. 13, 1916, was positive and continued so until March 16, when special cultures were begun. Positive cultures were now confined to the tonsils and the visible mass of adenoids. Cultures taken from the nasal mucous membranes were negative. Total cultures numbering twenty-four and covering a period of thirty-nine days were taken. The patient is still under observation.

CASE 7.—Harry S., aged 29, a diphtheria carrier, entered the hospital Feb. 16, 1916, with facial erysipelas; the throat cultures were negative. A general culture was positive on February 27 and continued to be so until March 13, when special cultures were started. The organisms were now found present in cultures taken from the pharyngeal wall and from the nasopharynx, taken per os, but they were not found in cultures taken from both tonsils, anterior nasal passages, both right and left, and from the external auditory canal. This patient had been operated on for mastoid disease a few days before entering the Contagious Hospital. Positive cultures were obtained from the mastoid wound on three different days. The patient is still under observation. Total cultures numbering thirty-eight were taken, covering a period of thirty-eight days. It may be of interest to note that a long organism was present in this case. It has been thought that these organisms are more virulent than the short ones.

CASE 8.—Sarah S., aged 4, on Dec. 22, 1915, showed clinical nasal diphtheria, which cleared up in a few days without any antitoxin. The patient was detained because of exposure to chickenpox before entering the hospital. General routine throat culture was positive Jan. 26, 1916. Special cultures were begun February 2. They were taken with a swab, those from the tonsils and pillars, pharyngeal wall and lateral bands proving to be negative. The tonsils in this case were so large that it was impossible to reach the pharynx with a swab without touching them. A stiff platinum loop was substituted for the swab February 11. The cultures were now positive from both tonsils and negative from the pharyngeal wall and nose. Total cultures numbering thirty-three were taken, covering a period of seventy days.

CONCLUSION

1. All parts of the mucous membrane of the upper respiratory tract must be touched in making a satisfactory general culture.

2. The pharynx may be cultured and be negative for Klebs-Loeffler bacilli, but the organisms may be present in the nose or in the larynx and thus not be found except by special technic in culture work. Or as in Case 1, one tonsil may give positive cultures while all other portions of the mucous membranes may be negative. Nose bleed and hoarseness or loss of voice should attract attention to the nose or larynx.

3. Sterile cotton swabs are found to be most adaptable for getting culture material from all parts of the upper respiratory tract. Second in preference for culture taking is a platinum loop. The platinum wire must be quite heavy and stiff in order to prevent its curling and bending. It can be used only in taking cultures from tonsils, pillars, posterior pharyngeal wall and lateral bands. It cannot be used in taking nose and laryngeal cultures because of danger of trauma to the mucous membrane.

4. Several cases in this series show the necessity of having more than one or two cultures to determine that diphtheria organisms are absent from the upper respiratory tract. In this hospital at least three negative cultures are required before a patient may be discharged or before a nurse may return to the main hospital for service.

5. This interesting and peculiar tendency of the diphtheria organisms to localize in one part of the upper respiratory tract should be an important factor in deciding on surgical or medical treatment to eliminate the organisms from this part.

INFANTILE SCURVY

III. ITS INFLUENCE ON GROWTH (LENGTH AND WEIGHT)*

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In two previous papers[1] on this subject it was shown that pasteurized milk, that is, milk heated to 145 F. for thirty minutes, gradually induces infantile scurvy, unless antiscorbutic diet is given in addition. The fact that this disorder quickly yielded to the substitution of raw for pasteurized milk, or to the addition to the diet of an ounce of orange juice, or the juice of orange peel, was regarded as satisfactory evidence of the true scorbutic nature of the disturbance. The type of malnutrition which gradually develops from a diet of pasteurized milk may be termed subacute scurvy, as it takes some months to develop and, as a rule, does not manifest the pronounced symptoms characteristic of the classic case. In some instances, however, we encounter subperiosteal hemorrhages and the hemorrhagic gums typical of this disorder. That infantile scurvy is not met with more commonly, in view of the widespread use of pasteurized milk as a food for infants, may be ascribed to the fact that orange juice or other antiscorbutic food is so generally given in addition to milk. In other words, although pasteurized milk is to be recommended on account of the safety which it affords, it must be regarded as an incomplete food for infants. That the disease developing under these conditions is subacute in nature is to be attributed to the fact that the "vitamins," which are not overabundant in commercial milk, are not entirely destroyed by pasteurization, so that the infant receives day by day a small amount of these essential substances.

It will be remembered that these cases of scurvy arose in an institution where the use of orange juice was discontinued, in view of the report of the Commission on Milk Standards to the effect that milk does not suffer a destruction of enzymes or other chemical constituents in the course of pasteurization. In the first paper the nature of the hemorrhagic condition was studied, the question of involvement of the blood or of the blood vessels. In the subsequent paper the symptoms of infantile scurvy were shown to bear an intimate relationship to those

* Submitted for publication May 2, 1916.
* Presented in abstract form before the Society of Experimental Biology and Medicine, Dec. 1, 1915. (Vol. XIII, No. 3, Proceedings.)

1. Hess, A. F., and Fish, M.: Am. Jour. Dis. Child., December, 1914, viii, 386. Hess, A. F.: Jour. Am. Med. Assn., 1915, lxv, 1003.

of other deficiency diseases, more particularly beriberi. It was pointed out that scurvy should no longer be regarded clinically as a disorder characterized merely by hemorrhages, nor from a pathologic viewpoint merely as one manifesting changes in the bones, but that signs and symptoms of involvement of the heart (enlargement of the right ventricle and tachycardia) and of the peripheral nerves are also evident, so that a broader aspect is demanded. This paper, the third in the series, which is based mainly on the same cases which formed the groundwork of the previous studies, shows how these infants reacted in their growth to alterations in diet, how they grew on a diet consisting of pasteurized milk, sugar and cereal, when they were at the same time receiving orange juice, when the orange juice was discontinued, and when this juice or the juice of the orange peel was again added to the diet. These infants offered a particularly favorable opportunity for observations of this kind because they entered the institution at an early age and remained there for one or more years, and also because they were most carefully observed, weighed daily and measured on admission and every fortnight subsequently. It was thus possible to chart their growth for more than a year and to compare their progress with that of the other infants in the institution. As far as we are aware, no study of this kind has been attempted in connection with scurvy, although it has long been known that the development of the scorbutic condition is generally accompanied by a cessation of gain in weight. Particular interest would seem to be given this investigation as the subacute type of scurvy must be considered not only the most common form of the disorder, but that which passes most often unrecognized. The opportunity presented itself to probe farther into this question of growth and to determine whether there is not likewise a stunting of the normal increment of the skeleton, an interference with the increase in length. This part of the study was judged to be of greater biologic interest than a mere observation of the effect on weight, as it is well established that infants are particularly tenacious of their impulse to grow in length, and are not readily affected in this respect by nutritional disorders, even such as reach a considerable degree of intensity. As Birk[2] has shown, extreme undernourishment is necessary to bring about stunting. In animals, Aron[3] demonstrated that lack of nutrition led to a decrease of the fat and of the muscle in the body, but that under such conditions the skeleton continued to grow, and the ash content of the body to increase. If, therefore, this function of the body were affected, we must consider that the metabolism must be profoundly disturbed, and the deficiency of nutritional substances far reaching.

2. Birk, W.: Berl. klin. Wchnschr., 1911, No. 27.

3. Aron, H.: Biochemie des Wachstums des Menschen und der hoeheren Tiere, Gustav Fischer, 1913, p. 58.

First, as to growth measured by weight, the various charts (Figs. 1 to 4) accompanying this article show the effect in this regard. It will be noted that although the infants continued to gain for a month or two following the discontinuance of orange juice, a decided flattening of the weight curve gradually set in, an almost constant level being maintained for weeks and months. This stationary period persisted until antiscorbutic food was once more added to the diet, when a sudden rise made itself evident. This gradual cessation of gain and sharp reaction may be stated to have been the rule, as there was but one instance in which an infant continued to gain for months in spite of the lack of antiscorbutic food. It will be seen from these charts that there was no permanent retardation of weight; in other words, the growth impulse of the body remained unimpaired and had been merely in an inactive or quiescent state. When orange juice was given once more, the rate of growth was abnormally great. There was supergrowth. Furthermore, after a period of extended observation of six months or more, it has been found that this increased rate of growth is maintained until the infant reaches a weight normal for its age. These charts seem to require but little elucidation. We may add that orange juice and orange peel juice, an infusion of one ounce of orange peel in two ounces of water, were equally efficacious in bringing about a sharp increase in weight, and that these substances apparently did not lose their potency by being boiled.

Two cases should be mentioned especially, as they represent a clinical aspect somewhat different from the others. These infants were under 6 months of age and had never received orange juice. It was possible in these instances to observe for how long a period infants will continue to gain steadily in weight on pasteurized milk before it becomes necessary to add orange juice to their diet, and to judge whether they gradually manifest a lack of gain which can be obviated by giving an antiscorbutic foodstuff. It was found that at about the seventh or eighth month a gradual but definite falling off was evident, and that this deficiency was at once corrected by adding orange juice. Figure 3 represented this condition very clearly. We note here an infant who gained about one half pound during the months of February, March, April and May, but who in June, when given boiled orange peel juice or orange juice, gained two pounds within a month. There were no other scorbutic signs or symptoms and no loss of appetite during the months of February and March, although the baby was suffering from a progressive form of scurvy. It is probable that this case and a similar one which we encountered are not solitary instances of this kind of reaction, but that many infants fail to gain at this period, the third quarter of the first year of life, for the want of this essential substance in their food, and that unconsciously this deficiency is reme-

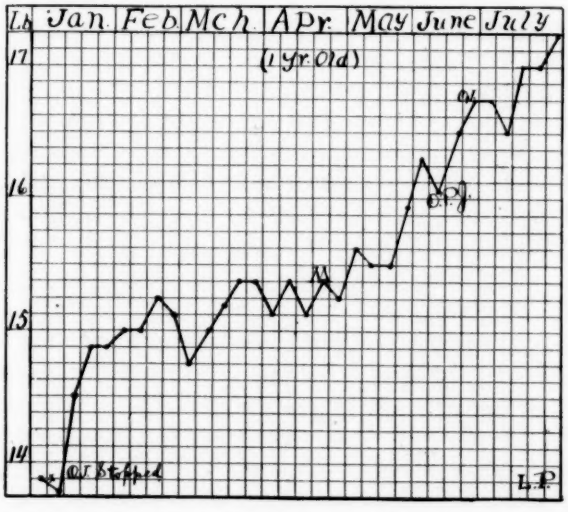

Fig. 1.—Marked gain in weight on orange peel juice and orange juice after lack of gain for three months.

In this and the following figures *O. J.* indicates orange juice; *M.* wheat middlings, and *O. P. J.* orange peel juice.

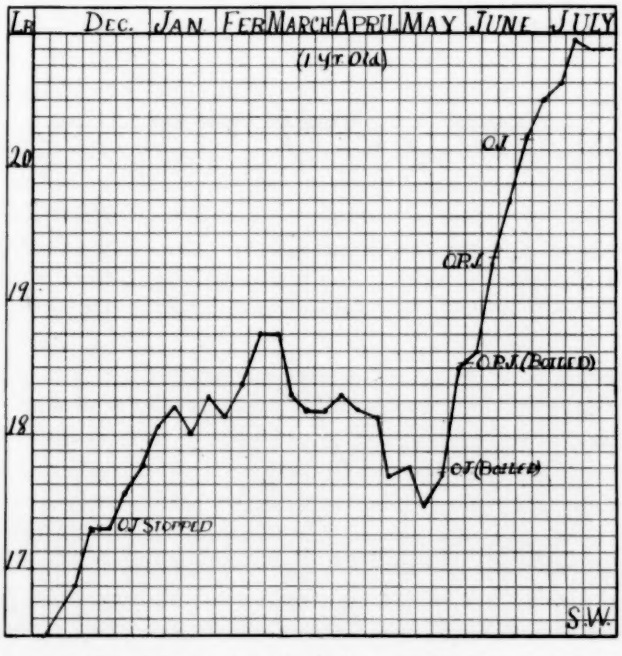

Fig. 2.—Loss of weight checked by boiled orange juice and boiled juice of orange peel.

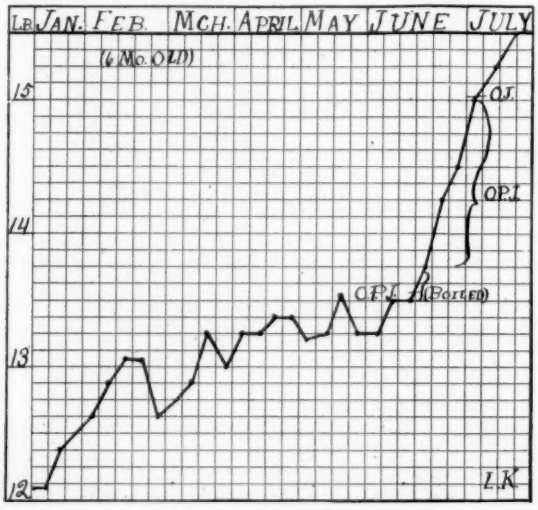

Fig. 3.—Latent scurvy in young infant who had never received orange juice. Scorbutic nature of growth disorder proved by sharp rise in weight on addition of antiscorbutic food to the dietary of pasteurized milk.

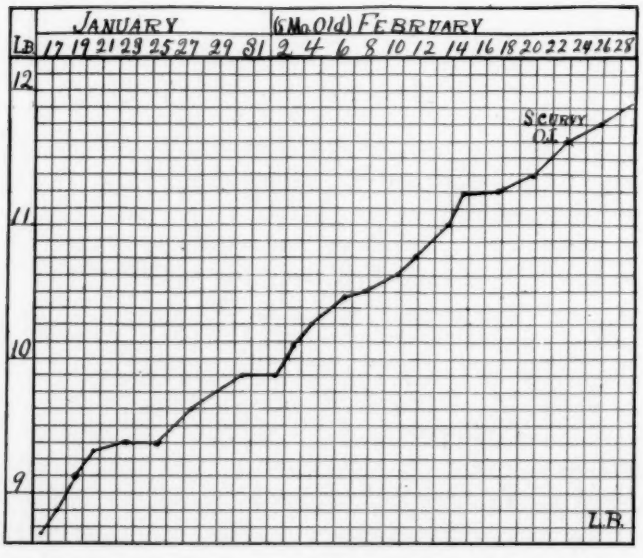

Fig. 4.—Development of scurvy in spite of normal gain in weight in a baby who had been underfed since birth.

died by adding vegetables and fruit to their dietary. We would therefore urge that antiscorbutics, for instance orange juice, be given infants at an early age. At present, the rule may be said to be to add fruit juices to the dietary at about the sixth month. This period has been chosen as the proper one, probably because scurvy rarely develops during the first half year of life. However, when we reflect that this time incidence is due to the fact that the infant is protected for the first few months of life by the supply of antiscorbutic material which it has received from the mother, and that there must be a constant negative balance of these essential substances dating from the earliest beginning of artificial feeding, it would seem as if a corrective dietary, that is to say, an antiscorbutic food, should be given as soon as practicable. There is no reason that I know of why an infant should not receive orange juice when it is a month old, and, as we have seen, there are strong arguments in favor of such a procedure.

It may be enunciated as a rule, embracing a few exceptions, that the development of the scorbutic state is generally accompanied by a failure to gain in weight. Under certain conditions, however, the weight may follow a perfectly normal course during the entire period. This observation has, from time to time, been made by others, but has received no particular consideration. It may be well therefore to cite in some detail a case of this kind, and discuss one cause of this apparently paradoxical course of events. Figure 4 illustrates this clinical paradox. The baby to whom it refers was admitted to the institution in January and was stated to be only four months of age. As a matter of fact, as we learned later, he was seven and a half months old. Toward the end of February, when he had been in the institution two months, and in spite of constant and normal gain in weight, to our surprise he manifested unmistakable signs of scurvy—peridental hemorrhage over the upper incisor teeth, which were erupting, and tenderness of the lower ends of the femora. The scorbutic nature of these signs were substantiated by their prompt subsidence on the administration of orange juice.

How is this phenomenon to be explained, normal growth during the development of scurvy, one of the classical nutritional disorders of infancy? The solution is to be found in a careful consideration of the previous diet of the baby. On investigation we found that it was born on June 5, 1915, at term, weighing six pounds, but was never nursed. For the first two weeks it received an indefinite formula prepared by the mother. From June 21 to August 19, that is, for a period of about two months, it was given a formula composed of one-fourth milk, three-fourths water, and 1.5 per cent. sugar, two ounces every three hours. In other words, it was greatly underfed for these two months. In August it weighed 8 pounds, 5 ounces. From August 19 to 27 the

formula was 30 ounces water, 12 ounces milk, and about 1 per cent sugar, four ounces being fed every three hours. This resulted in loss of weight, the baby weighing 7 pounds 15 ounces. On September 7 the formula was made one-half milk, one-half water and 1 per cent. sugar, four ounces every three hours. The underfeeding continued. On December 5 it was transferred to a hospital, where it was given a malt soup preparation for one month. It developed gastro-enteritis on January 17. As the chart shows, the child was admitted to the Hebrew Infant Asylum, weighing about 8¾ pounds at the age of 7½ months.

If we consider the feeding of this infant, we realize that it had been almost continuously undernourished, receiving an insufficient amount of fats and carbohydrates at almost all times. At the asylum the baby was put on Schloss milk, a food containing about 4 per cent. fat and about 6 or 7 per cent. carbohydrates, seven feedings of 4 ounces in the twenty-four hours. On this it remained and, as will be seen, made steady gains until it developed scurvy toward the end of February.

This baby must be regarded as having been partially starved throughout the period following birth, with the result that on receiving a diet rich in fats and carbohydrates, foodstuffs which bring about a marked increase in weight, the reaction of the tissues was necessarily prompt and prolonged. It explains this type of case, showing that if an infant has received insufficient food, we can compel growth simply by increasing the caloric value of the dietary, notwithstanding the fact that scurvy is developing day by day. It also brings out the salient fact that more than a single cause exists leading to a repression of growth, and that therefore lack of growth must be differentiated if it is to form the basis of study. A deficiency of scurvy vitamins is one cause, lack of sufficient or adequate food is another, and, no doubt, there are still other inciting factors. Whether or not growth occurs, and to what extent, depends on the resultant stimulation which can be brought about by these various impulses. In this instance the primary growth impulse which follows a diet containing a sufficient number of calories had been held in abeyance for so many months through starvation, that when it was once more stimulated to full activity by a liberal diet, it was able to overcome the growth repression which ordinarily accompanies the development of the scorbutic condition.[4]

The foregoing illustration must make it clear that growth does not play an essential or elemental part in the constitution of infantile

4. This phenomenon probably also holds good for scurvy in the adult. A scorbutic condition may result from a lack of fresh food; but if the person has been markedly underfed, there may be a gain in weight coincident with the development of the scorbutic condition, provided liberal diet is given, including plenty of carbohydrate and fat.

scurvy. It must likewise render it evident that this study cannot be regarded as concerned with growth in general, but only with the effect of infantile scurvy on growth, as various disorders may affect this function. That such is the case is well known to clinicians and has been shown admirably in relation to animals in the recent investigations of Osborne and Mendel, of McCollum and others, which showed that growth was retarded or stimulated at will by means of diet. The results of these workers cannot, however, be considered as having any bearing on scurvy, for scurvy and growth stunting are by no means identical, either in animals or in infants. It would seem that these remarks are timely in view of a recently published study by McCollum and Davis,[5] in which they show that the growth factor in milk is closely linked to its casein content, and preface their report by drawing an analogy to infantile scurvy, although apparently none of the animals showed any signs of a scorbutic condition.

Looking at this question from the reverse point of view, one sees clearly that factors which stimulate growth are not necessarily antiscorbutic. For example, McCollum and Davis[6] showed that butter fat, even after it had been heated to a high degree, was able to induce growth, and Osborne and Mendel[7] showed that this fat can be subjected to steam and not lose its growth producing power. It is nevertheless evident that butter fat in pasteurized milk does not possess sufficient antiscorbutic properties to prevent the development of scurvy, and that substances such as lysin and tryptophan, which possess marked growth promoting power, and which were present in considerable amount in our diet, were unable to make up for the dietary deficiency and bring about growth. Furthermore, cod liver oil has been found to possess growth-promoting qualities of a high degree, but there is no question that this substance, as has been shown elsewhere,[1] is incapable of preventing the development or accomplish the cure of scurvy. Before reporting additional observations as to the influence of scurvy on growth, let me add that all of the infants under consideration obtained plenty of milk, and all the older ones received cereal in addition. Particular attention was given to their obtaining a sufficient quantity, so that the factor of an insufficient diet might not enter into the question. To this end, when orange juice was discontinued, more cereal was given or the strength of the milk mixture was increased in many instances. In those cases in which there was loss of appetite, particular effort was made to have the infants take the full quantity of food, and, although the total amount consumed in many cases was not quite as much as when they were well, it nevertheless equaled that

5. McCollum, E. V., and Davis, M.: Jour. Biol. Chem., November, 1915, p. 247.
6. McCollum, E. V., and Davis, M.: Jour. Biol. Chem., 1913, xv, 167.
7. Osborne, T. B., and Mendel, L. F.: Jour. Biol. Chem., May, 1915, p. 381.

which many infants in the institution consume and on which they continue to grow.

There is no doubt that considerable of the supergrowth which so clearly follows the giving of orange juice or its equivalent is due to an increased consumption of food. However, it would be a mistake to consider that such is entirely the case. We have reproduced two charts to illustrate this point. The first (Fig. 5) is a daily weight chart of an infant with mild scurvy, and shows the period preceding as well as

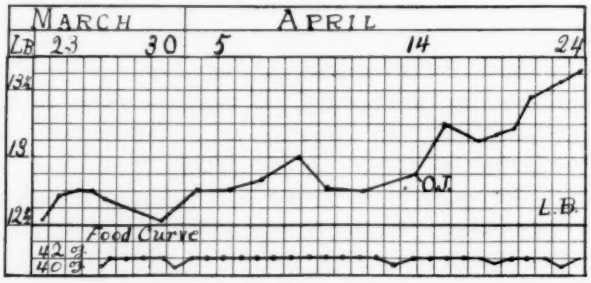

Fig. 5.—Same case as preceding. Detailed chart showing marked gain following the addition of an antiscorbutic to the diet, although amount of food remained the same.

Gain of 5 ounces in three weeks before, and 12 ounces in ten days after orange juice was given.

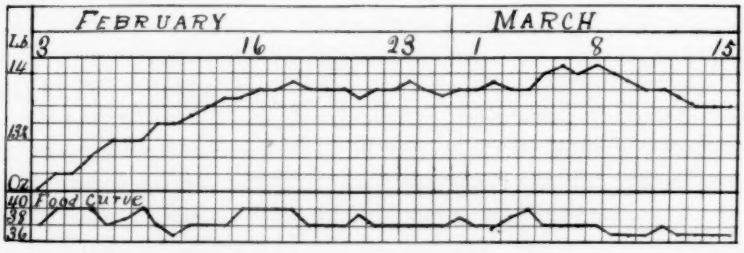

Fig. 6.—Section of a weight chart showing daily weighings during the period when gain still continued and when stationary plane was reached.

Note that the same amount of food was taken daily during the first two weeks of February, when the infant gained 12 ounces, as from the middle of February to the middle of March, when there was no gain whatever.

This baby had latent scurvy and responded promptly to orange juice.

that following the giving of orange juice, together with the food intake (Schloss milk). Although it will be seen that there was no change in the amount of milk taken before and after giving orange juice, there was a marked difference in the gain; the infant increased only 5 ounces in weight during the three weeks in which it did not obtain orange juice, and 12 ounces in ten days following its addition to the diet.

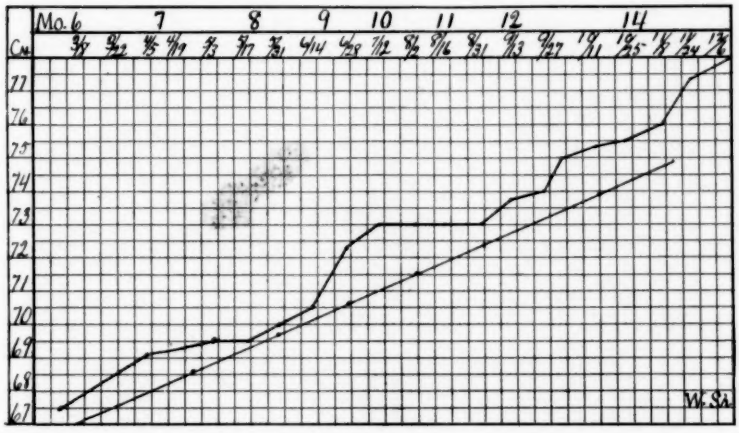

Fig. 7.—Growth in length from the sixth to the fifteenth month of healthy baby receiving orange juice. The lower line represents the average growth.

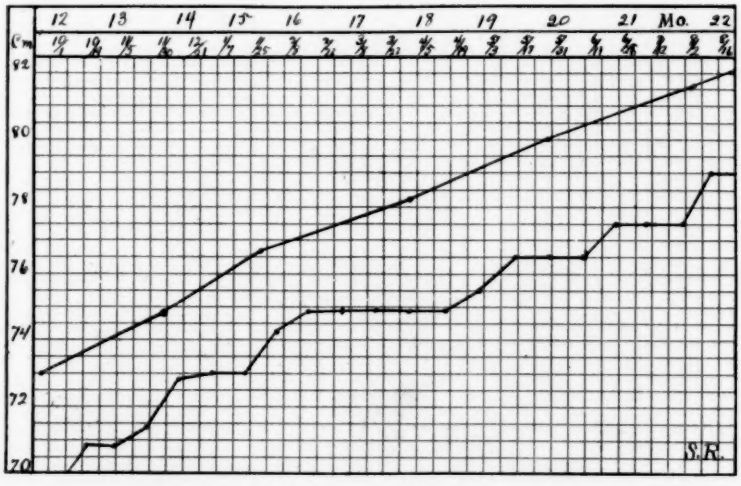

Fig. 8.—Growth in length from the twelfth to the twenty-second month of a very small, healthy baby receiving orange juice.

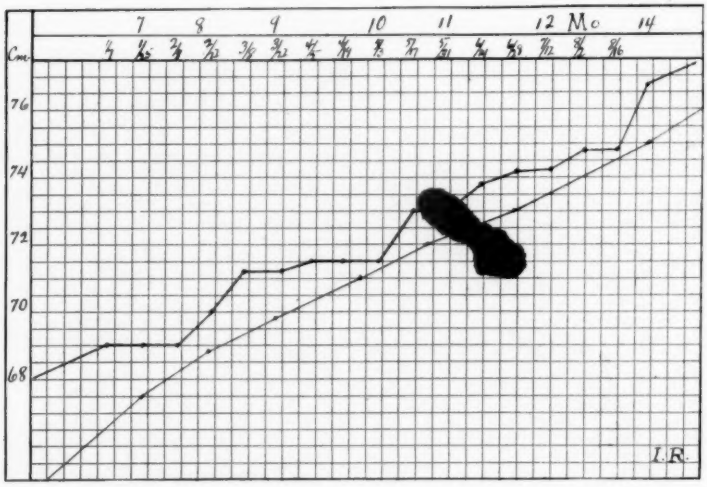

Fig. 9.—Growth in length from the seventh to the fourteenth month of a large healthy baby receiving orange juice.

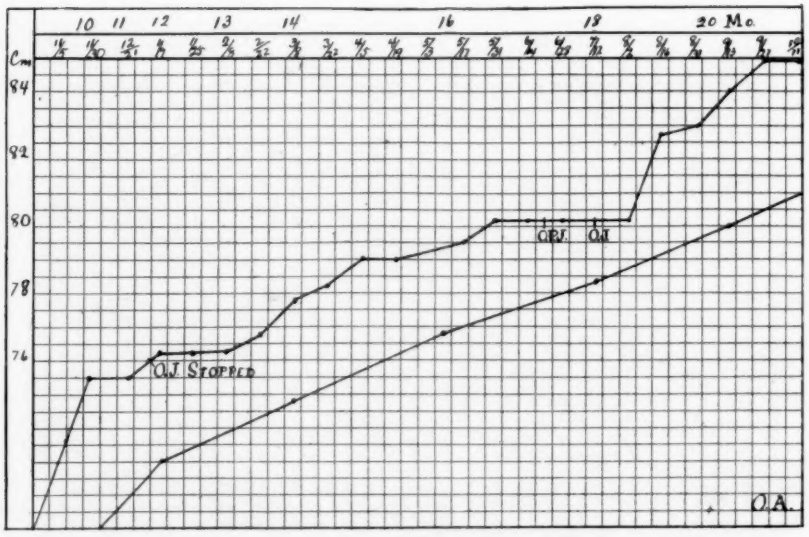

Fig. 10.—Growth in length for a period of five months during which no orange juice was given, compared with subsequent months when it was again added to the diet.

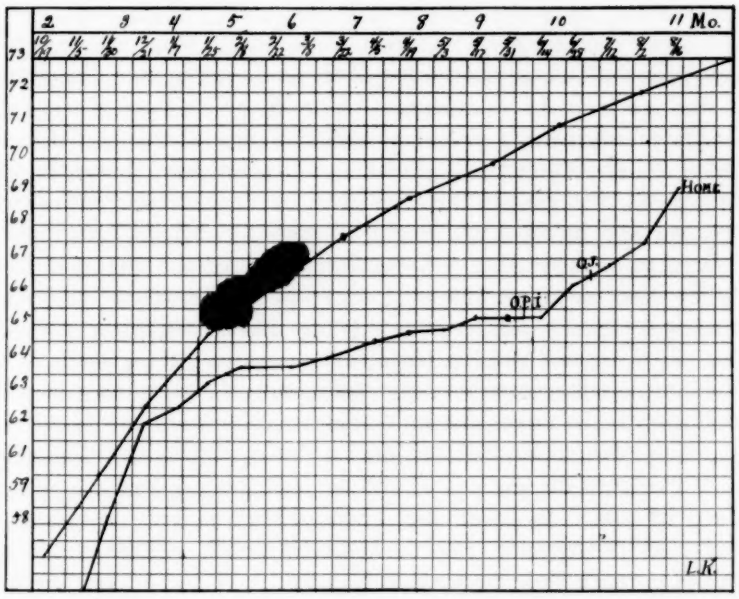

Fig. 11.—Length chart of young infant (illustrated in Fig. 3) who had never received orange juice. Marked reaction in growth in length when an antiscorbutic was added to the diet.

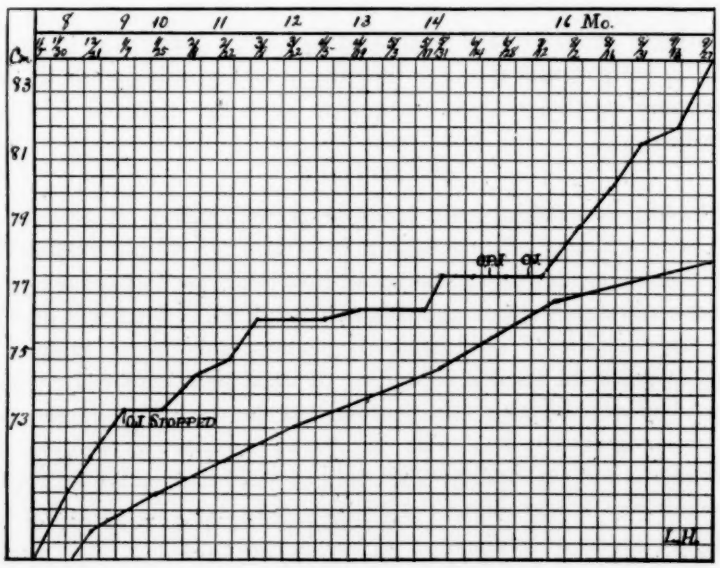

Fig. 12.—Showing retardation of growth in length during the period when no orange juice was given, and supergrowth when it was given once more.

Figure 6 shows another aspect of this question. It demonstrates that the period of gradual growth stagnation, on which infants fed entirely on pasteurized milk enter as the result of not receiving an antiscorbutic, is not due to a lack of food. Here we note the gradual inception of this stationary phase, from a period of gain, in spite of the fact that the intake of food remained undiminished. It is evident, therefore, that neither the lack of gain in the course of the development of infantile scurvy, nor the increase of weight coincident with its cure, can be considered to be dependent on the caloric value of the dietary.

As has been mentioned above, a study of the growth in length was also carried out, the measurements being taken fortnightly for over a year. In order to furnish a basis for comparison, the growth of ten normal infants who received orange juice, but otherwise the same diet, was followed at the same time. The charts which we reproduce clearly bring out the distinction between the two groups of cases. Figures 7, 8 and 9 illustrate the growth of the normal infants, and constitute a standard by which to judge the others. They portray a consistent, alhough slightly irregular, growth month by month. Quite in contrast to these curves are those depicted in Figures 10, 11 and 12, representing three infants who did not receive orange juice from January to May.

Figure 11, which represents growth in length complements Figure 3, representing growth in weight, and illustrates the case of a young baby who had never received orange juice, and developed a latent or rudimentary form of scurvy when about eight months of age. These three cases, when contrasted with the normals, leave no question that the scorbutic condition has a decided effect on growth in length as well as in weight, and that this impulse remains unimpaired in both respects and capable of quick response when the essential foodstuff is furnished.

CONCLUSIONS

Although pasteurized milk is to be recommended on account of the security which it affords against infection, we should realize that it is an incomplete food. Unless an antiscorbutic, such as orange juice, the juice of orange peel, or potato water is added, infants will develop scurvy on this diet. This form of scurvy takes some months to develop and may be termed subacute. It must be considered not only the most common form of this disorder, but the one which passes most often unrecognized. In order to guard against it, infants fed exclusively on a diet of pasteurized milk should be given antiscorbutics far earlier than is at present the custom, even as early as at the end of the first month of life.

In the course of the development of infantile scurvy, growth, both in weight and in length, is markedly affected. Under these conditions,

weight ceases to increase, and a stationary plane is maintained for weeks or for months. There is a quick response, however, on the administration of orange juice or its equivalent, indeed supergrowth is thereupon frequently manifested. If, however, an infant has been underfed, an increase in weight may continue throughout the development of the scorbutic condition. Cessation of growth, as well as marked increase in growth, may manifest themselves, although the caloric value of the food remains unchanged, depending merely on the withholding or the addition of essential foodstuffs to the diet.

Measurements showed that growth in length is also retarded during the protracted development of infantile scurvy. This is of greater biologic interest, as simple malnutrition usually does not affect this function in the infant. In this particular, supergrowth also follows the addition of the essential foodstuff, showing that the growth impulse has remained uninjured and has been merely held in abeyance.

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PROGRESS IN PEDIATRICS

RESUME ON INFECTIOUS DISEASES *

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The chief general advances made in contagious diseases in the past few years are the wider use of the so-called aseptic technic with the handling of cases, based on the notions of Grancher, and a tendency to attempt active immunization as a means of either preventing these diseases or forestalling their manifestation in a severe form.

HOSPITAL CARE

The newer view of the hospital care of patients with contagious diseases admits as possible and desirable their maintenance in all cases in the same building or even in the same ward with general nursing. Its success seems to depend almost entirely on the conscientiousness with which doctors and nurses carry out the few simple technical precautions, which are in fact almost identical with those observed in the surgical operating room.

The article by Richardson[1] gives a brief résumé of work previously done, especially in English hospitals, with description of hospital and technic used. Three per cent. cross infections is reported as the average. Similar hospitals in this country are in operation at the University of Michigan,[2] in Evanston,[3] and in Chicago.[4]

One of the others under construction is to be at Iowa City. An attempt was made to introduce this system in the new children clinic of Vienna,[5] and over 10 per cent. of cross infections were reported, the high figure being due no doubt to the well-known inferiority of continental nurses. Connell[6] describes the Monsall Hospital, Manchester, where this same method is being used. There have been as yet no official reports from the newer hospitals, although at Ann Arbor the percentage of cross infections during the

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* From the Department of Pediatrics, University of Michigan, Ann Arbor.

1. Richardson, D. L.: Jour. Am. Med. Assn., 1913, lxi, 1882.
2. Tr. Clin. Soc. Univ. Mich., 1913-1914, v, 90.
3. Sturm, M. J.: Mod. Hosp., iii, 3.
4. Durand Hospital.
5. Von Pirquet, C.: Ztschr. f. Kinderh., 1912, v, 213.
6. Connell, W. T.: Canad. Med. Assn. Jour., May, 1912, xli, 594.

first year was about 2. Phillips[7] urges the early isolation of all patients with mild or severe cases. In a series of 900 patients taken care of by the aseptic method there were but two cross infections.

Disinfection after contagious diseases has been discontinued in New York for four years. Chapin[8] shows that, in the instances of diphtheria and scarlet fever, recurrences have not increased in number, being 1.53 per cent. after 1908 and 1.48 per cent. before in scarlet fever, and 1.75 per cent. after 1908 and 1.71 per cent. before in diphtheria. Bedding disinfection is also dispensed with.

CHICKENPOX

Greeley[9] describes what he believes to be the etiologic agent of chickenpox, smallpox, and vaccinia. This is a sporothrix which corresponds to the *cytorrhyctes variolae* (Councilman). It passes through the Berkefeld filter No. 5 and does not grow on artificial media. Mycelial growth is said to be obtainable.

Kling[10] is the first to have successfully inoculated against varicella. He took the contents of the vesicle of a case at the height of the disease and injected it intradermally in fifty-eight patients, avoiding when possible the drawing of blood. On the eighth day one, usually more, small, red papules appeared. These suggested the lesions seen in cowpox. After a day or so a small, raised, red zone developed about these papules, from which vesicles appeared, which dried up in three or four days, the scab of which did not disappear for two or three weeks. The material from this vesicle could be used for inoculating other nonimmune individuals. Occasional rise of temperature was reported, but rarely illness or general rash. It is interesting to note that in several patients previously inoculated with cowpox vaccine a positive result was obtained, further evidence of the nonidentity of the two viruses. Of the patients inoculated, none developed chickenpox, although they had been exposed. Handrick[11] attempted to repeat this work, using the percutaneous method, with negative results. Tieche[12] describes a simple method of differentiating between chickenpox and variola, which depends on the fact that the intradermal inoculation of material from the smallpox lesion will give a positive reaction in the immunized individual, that is to say, vaccinated, whereas no reaction is obtained with the content of the varicella vesicle. By heating the suspected material for five minutes at

7. Phillips, C. H.: Brit. Med. Jour., 1912, No. 2694, p. 357.
8. Chapin: Medical Officer, 1913, ix, 218.
9. Greeley, H.: Med. Rec., New York, 1914, lxxxvi, 204.
10. Kling, C. A.: Berl. klin. Wchnschr., 1913, l, 2083.
11. Handrich, E.: Monatschr. f. Kinderh., 1914, xiii, 242.
12. Tieche: Cor.-Bl. f. schweiz. Aerzte, 1913, xliii, 735, 779; Ibid., 1914, xliv, 1121.

80 F. an earlier reaction was obtained. These tests were done by the experimenter on himself.

Besides these articles several clinical reports may be quoted. For example, Heim[13] tells of a family in which the mother had herpes zoster. Some weeks after this both children had measles with zoster-like arrangement of the lesions. Lereboullet and Moricand[14] report a case of varicella contracted at birth from the mother, the disease appearing fourteen days after birth. Lentz[15] tells of an instance of indirect transmission in which the child apparently infected its two sisters and mother with the disease and later itself became infected from these patients, thus carrying the disease without infecting itself. Three cases of acute appendicitis occurring during the course of measles are reported by Perier.[16] Storrie[17] has encountered two cases of hemorrhagic and gangrenous varicella. Krause[18] reports cases of varicella in adults, which he believes to be very rare. The diagnosis was verified by the method of Tieche. Lilienthal[19] reports six cases of varicella in adults, diagnosed as syphilis.

EPIDEMIC PAROTITIS

Little work of importance is reported on this subject. Feiling[20] studied the blood and spinal fluid in forty cases. He noted a slight absolute and relative increase of the white corpuscles and an early increase of the lymphocytes. In one case orchitis and leukopenia, with relative increase of polymorphonuclears, were found. The spinal fluid was studied when meningeal symptoms, such as vomiting, amblyopia, drowsiness and loss of patellar reflexes, were present. The fluid was found to be colorless and slightly turbid, with 2,500 white blood cells per cubic millimeter, of which 96 per cent. were mononuclears. Barach[21] studied the blood and found a leukopenia of 5,000 to 600 cells at the outset of the disease and over 48,000 at the height. With the subsiding of the parotid tumor the leukocytes tend to increase. He says that the lymphocytes are increased in number while the polymorphonuclears become fewer. The eosinophils disappear, to return later in greater number than normal. Friedjung[22] reports a case of recurrence of mumps in a 15-month-old baby after an interval of slightly over four months.

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13. Heim, P.: Berl. klin. Wchnschr., 1912, xlix, 2349.
14. Lereboullet, P., and Moricand, I.: Arch. de méd. d. enfants, 1914, xvii, 288.
15. Lentz, O.: Deutsch. med. Wchnschr., 1913, xxxix, 1148.
16. Perier, E.: Ann. de med. et chir. inf., 1914, xviii, 7.
17. Storrie, H. C.: Brit. Jour. Child. Dis., 1914, xi, 62.
18. Krause, P.: Deutsch. med. Wchnschr., 1913, xxxix, 881.
19. Lilienthal, L.: Deutsch. med. Wchnschr., 1913, xxxix, 1247.
20. Feiling, A.: Lancet, London, 1913, No. 4689, p. 71.
21. Barach, J. H.: Arch. Int. Med., 1914, xii, 791.
22. Friedjung, J. K.: Jahrb. f. Kinderh., 1913, lxxvii, 197.

The investigation of mumps in England by H. M. Gordon[23] shows that the highest mortality occurs in patients under 5 years and especially under 1 year. Gordon[24] also gives the pathologic findings in four fatal cases of mumps, the patients being from 2 to 4 years of age, death coming early, with a clinical picture of meningoencephalitis. The lumbar fluid showed increased pressure, with lymphocytosis. The salivary glands were clinically negative, but on histologic examination they showed a marked interstitial inflammation in the perivascular and excretory duct region. On Berkefeld filtration the material obtained from some of these cases seemed capable of producing meningitis and parotitis in monkeys. Acker[25] reports two cases complicated with meningitis. Dracinski and Mehlmann[26] have seen three cases of pancreatitis complicating mumps. The onset was with fever and headache and the patient presented severe symptoms of collapse, epigastric pain, vomiting, Cheyne-Stokes breathing, delirium, loss of patellar reflexes and acetonuria. Two cases of oöphoritis are reported by Brooks.[27] In one of these an abscess formed requiring incision. In the other both breasts atrophied. Conception did not take place in either case within the five years the patients were under observation.

MEASLES

Epidemiology and Prophylaxis.—Rohmer[28] analyzed a hospital epidemic and concluded that in the average case measles is infectious for at least seven days, that is, during the period of invasion and exanthem, but not during desquamation. The patients were all confined to their beds and the disease consequently carried from one to the other by the nurses or by utensils. Raffie[29] shows quite conclusively that school closure when measles appears is the most effectual method of controlling the disease. Thus, of 4,470 children, 2,180 were susceptible. There were 618 cases of measles before school closed and only 140 within fourteen days after closing, while but seventy-five new infections developed during the third week. Cohn[30] is of the same opinion, urging that all who have not had the disease be excluded at least fourteen days. Craster,[31] in an interesting study of measles among immigrant children, showed that most cases appeared in June. The largest complication average a case mortality occurred in infant. The

23. Gordon, H. M.: Jour. Am. Med. Assn., 1914, lxiii, 414.
24. Gordon, H. M.: Lancet, London, 1913, clxxxv, 275.
25. Acker, G. N.: Am. Jour. Dis. Child., 1914, vi, 399.
26. Dracinski, N., and Mehlmann, J.: Deutsch. med. Wchnschr., 1914, xl, 1566.
27. Brooks, H.: Jour. Am. Med. Assn., 1913, lx, 359.
28. Rohmer, P.: Jahrb. f. Kinderh., 1912, lxxv, 78.
29. Raffie, A. B.: Lancet, London, 1912, clxxxi, 294.
30. Cohn, M.: Ztschr. f. Schulgsndhtpfl., 1914, pp. 654, 723.
31. Craster, C. V.: Am. Jour. Dis. Child., 1914, vi, 122.

seasonal prevalence of complication was greatest in winter (December), with the case mortality highest in January. Otitis was the most frequent complication.

Corney[32] describes an epidemic of measles in an island of the South Sea, which was like the classic outbreak in the Faroe Islands. Of the nearly 2,000 inhabitants one fourth died, the death rate between the years up to 5 and between 20 and 25 years being greatest. Of the fatal sequelae bronchopneumonia, phthisis and ileocolitis were prominent. Mery and Malhene[33] emphasized the fact that this disease has the greatest mortality in asylums and in foundlings' homes. For example, the total mortality in the institutions of France studied was 11 per cent. of the inmates. If the deaths from measles had been excluded, the mortality would have been 5 per cent. Kilbourne[34] reports 600 cases of measles occurring among adults in the Columbus barracks. The mortality was 5 per cent. This figure should be compared with the report of Crum,[35] who shows the mortality in patients over 20 years to be 0.3 per cent.; the mortality in patients from 1 to 4 years is 1 per cent., while in those under 1 year of age it is 3.5 per cent. The lowest mortality is found between the years of 5 and 9, when 0.2 per cent. is given. The lowest mortality thus occurs in patients infected between the ages of 5 and 19 years. These figures should guide us in quarantine and prophylaxis.

Pathology.—The loss of allergy occurring during measles is shown in several new ways by recent investigations. Thus Koch[36] shows strikingly the relationship that the various stages of measles bear to the loss of the power to react against infection. In the days immediately before and after the appearance of the exanthem, most purulent and secreting processes temporarily cease, for example, the fistula of the cold abscess, the reaction of meningitis, and the cavity of empyema. During the period of the rash there is a failure to react to tuberculin and vaccine, serum rashes and psoriasis. In the week following the exanthem there is the well-known increased tendency to purulent processes and their spread, together with the liability to thrombosis, embolism, necrosis and gangrene. Neumark[37] reports a case of a 3-year-old child, who developed the rash of measles four days after being vaccinated. The first typical vesiculation was not noted until eleven days after scarification, a delay of about four or five days. The reaction was normal from that time on.

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32. Corney, B. G.: Brit. Jour. Child. Dis., 1913, x, 252.
33. Mery, H., and Malhene: Bull. Soc. de pédiat. de Paris, 1913, xv, 1.
34. Kilbourne, E. D.: Mil. Surgeon, 1912, xxxi, 294.
35. Crum, F. S.: Am. Pub. Health, 1914, iv, 289.
36. Koch, H.: Ztschr. f. Kinderh., 1914, xi, 267.

Tunnicliff[38] has found a distinct diminution of phagocytic activity of the leukocytes for streptococci, staphylococci and tubercle bacilli, during the period of the leukopenia, with the return to normal of the blood the phagocytic index also tended to increase. In cases of monkeys inoculated with the blood of measles patients a similar phenomenon is observed. Moltschanow[39] shows that the loss of tuberculin sensitiveness is independent of the fever and complications, but is in close association with the rash. Lucas and Prizer[40] and Nicolle and Conseil[41] verify the work of Hektoen and of Anderson and Goldberger by injecting the blood of measles patients intracerebrally and intraperitoneally.

The incubation period was found to be six days, the Koplik spots appearing on the average of four days later. The virus was transmitted from one ape to the second and from the second to the third. They assume that the virus is in the blood within twenty-four hours after the buccal spots appear and thirty-six hours after the beginning of the skin eruption. A leukopenia is found in the preeruptive stage. The latter observers also find the virus in the blood nine days after inoculation. C. von Pirquet[42] applies his theory of incubation to this disease. He assumes that the infecting micro-organisms enter the body and during incubation there is developed the so-called ergin, which has the character of an antibody. This takes part in the digestion of the invading micro-organisms, with the result that there is formed a toxic product, or apotoxin, which in turn produces the fever, enanthem, and exanthem. The quick death of the virus explains the definite and rapid ending of the disease. He believes also that the process of agglutination plays a part in the formation of the rash. Just why the apotoxin should appear first, and possibly in the greatest quantity, in the tissues of the head is not clearly explained. It seems necessary, however, that the tissues must be saturated with a certain amount of this substance and that, therefore, the regions with the richest blood supply receive the greatest amount of the antibody and so show the rash first.

Remembering the work of Pfeiffer on the toxicity of the urine in anaphylaxis, Aron and Sommerfeld[43] examined the urine in a series of cases of measles, intravenously injecting from 1 to 2 c.c. into a

38. Tunnicliff, R.: Am. Jour. Infect. Dis., 1912, xi, 474.
39. Moltschanow, B.: Russk. Vrach., 1911, No. 43; abstr., Jahrb. f. Kinderh., 1912, lxxi, 619.
40. Lucas and Prizer: Jour. Med. Research, April, 1912, xxvi, 181.
41. Nicolle, C., and Conseil, E.: Paris Letter, Jour. Am. Med. Assn., 1912, lviii, 289.
42. Von Pirquet, C.: Ztschr. f. Kinderh., 1913, vi, 1.
43. Aron, H., and Sommerfeld, P.: Deutsch. med. Wchnschr., 1912, xxxviii, 1733.

guinea-pig. While from 2 to 4 c.c. normal urine were well borne, 2 c.c. were stated to have been sufficient to produce quick death, with the symptoms of anaphylaxis. The substance is thermostable and dialyzable. There seems to be no relationship with the period of exanthem. The duration of excretion of the poison varies in different individuals. These investigators had negative results with the urine of patients with typhoid fever, pertussis, scarlet fever and diphtheria. The urine derived from a patient with serum exanthem and fourth disease gave positive results. Mautner[44] comes to a different conclusion, in that while the urine of measles patients was toxic, the same property was found in specimens voided by those infected with diphtheria, peritonitis, scarlet fever, valvular heart disease and arthritis.

Koch[45] describes a prodromal rash occurring in one fourth of his cases. This consisted in brownish-red, macular, illy defined spots, fleeting in character. They appeared chiefly on the face at the time or immediately after Koplik spots are seen. A further aid in the early diagnosis of measles comes from Grumann.[46] On both tonsils he found punctate and linear whitish swellings of about 3 mm. in length in the neighborhood of the lacunar depressions; these might also be seen on the more prominent follicular eminences. They seemed to appear either coincidentally with the Koplik spots or they might be present alone when the Koplik spots were absent, tending to precede the eruption by one or two days. He suggests that they may be superficial infiltrations or necroses. Lucas,[47] studying the blood in measles, found that the change in the differential picture took place about a week before the appearance of the characteristic symptoms. This consisted in the replacement of the normal relative mononuclears by a polynuclear increase. Some disintegrated cells were found, which, while not specific, when taken with the above transformation were of importance in epidemics, enabling earlier isolation without waiting for the appearance of the Koplik spots. Lutz[48] gives the necropsy findings in twenty-two cases of measles in which thrombus formation was encountered. Of these, six cases involved chiefly the pulmonary artery, while in two cases portal veins were partly obstructed.

Epidemiology and Mortality.—Feibelmann[49] reports two cases in which measles occurred a second time in the same individual. In one

44. Mautner, H. L.: Deutsch. med. Wchnschr., 1912, xxxviii, 1815.
45. Koch, H.: Ztschr. f. Kinderh., 1913, ix, 1.
46. Grumann, M.: München. med. Wchnschr., 1914, lx, 132.
47. Lucas, W. P.: Am. Jour. Dis. Child., 1914, vii, 149.
48. Lutz: Berl. klin. Wchnschr., 1913, l, 1566.
49. Feibelmann: Arch. f. Kinderh., 1911, lvii, 50.

of these it was impossible to determine whether the disease was to be recorded as a recurrence or a second infection. Koplik spots were found in each instance. Only five such cases are reported in the literature. On the other hand, Friedjung[50] reports three persons who, though definitely exposed, did not contract the disease, the patients now being 17, 19 and 19 years of age, respectively. It is possible that this is one of the rare cases of natural immunity. The striking influence of good hygienic surroundings on mortality is shown in the report of Maier.[51] Since the contagious patients have been moved into new quarters, the mortality from measles has been halved.

Complications and Sequelae.—Weill and Gardere[52] found an infectious erythema occurring in eight severe cases, of which four of the patients died. This erythema appeared at symmetrical points, distributed on the extremities, the trunk and abdomen not being involved except occasionally where the rash tended to become general. This was associated with ulceration in the mouth, in the cheek and in the pharynx, where Hutinel believes that secondary invaders found portals of entry. The mucous membrane lesions, however, were not necessarily present. There may be a succession of eruptions which are independent of the severity of the mucous membrane lesions or the severity of the disease. Clinical symptoms of the secondary infection may precede the rash. Griscom[53] found double choked disk occurring in a patient in the third week of the disease. Complete recovery took place. Morgenstern and Gruber[54] found multiple infarcts of the skin in a poorly nourished, rickety infant 1 year old. Multiple necrotic areas on the outer and lower side of the thigh below the gluteal fold were the chief lesions. Death occurred on the fifth day following the appearance of the rash. Delcourt[55] found two cases of subcutaneous emphysema as a complication of bronchopneumonia. This he interprets as being due to perforation of adherent lung. Ligabue[56] reports a case of subphrenic abscess following measles. Fischl[57] saw a case in which a hemorrhagic diathesis appeared following the disease with resulting enormous subcutaneous hemorrhages. Pertussis was also present. Galop[58] adds to the cases of gangrene of the limbs. Bronchopneumonia and enterocolitis were also present.

50. Friedjung, J. V.: Wien. med. Wchnschr., 1914, p. 939.
51. Maier, L.: München. med. Wchnschr., 1913, lx, 636.
52. Weill, E., and Gardere, C.: Rev. de méd., 1913, xxxiii, 545.
53. Griscom, M.: Ann. Ophth., 1912, xxi, 42.
54. Morgenstern and Gruber: Ztschr. f. Kinderh., 1914, xii, 100.
55. Delcourt: La Patholog. Infantile, 1914, xi, No. 1.
56. Ligabue, P.: Policlinico, Rome, xxi, No. 7.
57. Fischl: München. med. Wchnschr., 1912, lix, 621.
58. Galop, M.: Arch. de méd. d. enfants, 1914, xvii, 49.

Just before the appearance of the complications the popliteal pulse could not be felt, while the femoral pulse was still present.

Treatment.—Temporary interest was aroused by a rather extravagant statement of Milne,[59] who said that if as soon as possible after the outbreak of the rash pure eucalyptus oil were rubbed over the body of the patient twice a day and the tonsils swabbed every two hours with a solution of 10 per cent. phenol in oil for the first twenty-four hours, isolation became unnecessary and complications and secondary infections were prevented and disinfection rendered needless. Even the eating utensils were not sterilized. Elgart[60] repeated this and found that while it did not do all that its author predicted, it did seem to produce a diminished mortality. It is not uninteresting to find that he did not use phenol, finding that 50 per cent. lime water was as efficient and that he did not rub the body with the eucalyptus. Connolly[61] also believes that he has had help from this method, in that in comparative groups the mortality was but 5 per cent. among severe cases, whereas it was 11 per cent. in a similar group untreated. Marfan[62] shows that salvarsan given to a child as treatment for syphilis did not protect it against measles. This treatment has been more used in cases of scarlet fever, where further reference will be made to it.

GERMAN MEASLES

Outside of studies in hematology little of importance has been reported. Schwaer[63] finds a slight increase in the white cells with the mononuclears relatively greater in number. A leukopenia is not characteristic, as stated by many. The eosinophils, which disappear in measles at the height of the disease, are said to be constantly present in this disease. Hamburger[64] denies the report that he saw the eosinophils increase at the height of measles eruption. Saito[65] was fortunate enough to see an epidemic of 105 cases, including seventeen adults and six infants. The incubation period seemed to vary from fifteen days to twenty-three days. In only thirteen cases was the temperature over 100 F. The rash was of the characteristic papular type with anemic margins. Glandular enlargement was constant. The white blood count varied between 6,000 and 12,000 cells. Saito, in contrast with Schwaer, found the polynuclear cells relatively increased. Eosinophilia at the period of the fading rash was common, one case

59. Milne, R.: Lancet, London, 1911, p. 1070.
60. Elgart, J.: Med. Klin., 1913, ix, 1251.
61. Connolly, D. L.: Practitioner, London, 1912, lxxxix, 664.
62. Marfan, A. B.: Paris Letter, Jour. Am. Med. Assn., 1912, lviii, 1387.
63. Schwaer: München. med. Wchnschr., 1913, lx, 1203.
64. Hamburger, F.: München. med. Wchnschr., 1913, lx, 2120.
65. Saito, H.: Ztschr. f. Kinderh., 1914, x, 54.

of 42 per cent. being noted. No loss of susceptibility to tuberculin was made out as in cases of measles.

WHOOPING COUGH

Statistics and Epidemiology.—Emphasis has again, in the past few years, been laid on the high mortality from whooping cough. Morse[66] shows that while it causes the smallest number of deaths, 11.4 per 100,000, of the four important contagious diseases, still the percentage of mortality is very high and more attention should be paid to prophylaxis and isolation. Rucker[67] comments on the recent public health reports which state that 10,000 children a year are sacrificed to this disease. Pisek[68] finds the mortality in New York City to be over 10 per cent. of reported cases. According to his figures many of these died of tuberculosis. He urges special hospitals for the detention of such patients. An objection to the institutional care of such patients on the basis of the influence of proximity and the resulting suggestion is raised by Galisch.[69]

Experimental Work and Diagnosis.—Inaba[70] was able microscopically as well as culturally to demonstrate the Bordet-Gengou organism in 90 per cent. of his cases. A not uninteresting part of this report is the statement that the influenza bacillus differs from the organism of whooping cough in its cultural characteristics. The author finds that the whooping cough bacillus has more resistance and does not seem to have the same tendency to pleomorphism that the influenza bacillus has. He recognizes defibrinated goat's blood agar as the best medium for the cultivation of the bacteria. Manicatide[71] finds an organism which he denominates bacillus *Z* as the etiologic agent of whooping cough. This organism resembles the organism of influenza. He finds that the serum of both goats and sheep can be used for treatment and prophylaxis. The work surely needs further confirmation.

Diagnosis of the cough from similar clinical stages is determined by several authors by means of the reaction of complement deviation. Delcourt[72] finds it of special service. Friedlander and Wagner[73] use the fresh antigen, this being a seventy-two hour culture on ascitic agar. Fresh serum is also used. By this means they believe that they are able to diagnose the presence of the disease in its earlier stages, in

66. Morse, J. L.: Jour. Am. Med. Assn., 1913, lx, 1677.
67. Rucker: Jour. Am. Med. Assn., 1912, lix, 1882.
68. Pisek: New York Med. Jour., 1914, xcix, 970.
69. Galisch, A.: Med. Klin., 1912, viii, 488.
70. Inaba, I.: Ztschr. f. Kinderh., 1912, iv, 252.
71. Manicatide, M.: Ztschr. f. Kinderh., 1913, vii, 226.
72. Delcourt, A.: La Patholog. Infantile, 1912, ix, No. 1.
73. Friedlander, A., and Wagner, E. A.: Jour. Am. Med. Assn., 1914, lxii, 1008.

contradistinction to Bacher and Metchnikoff,[74] Bordet,[75] and Netter and Weill,[76] who were able, by employing the usual technic, to find a positive reaction only at the height of the disease or in convalescence. Thirty examinations on eighteen cases were positive in the paroxysmal stage; in three cases two positive results were found even in the catarrhal stage. Neurath[77] attempted to produce an intracutaneous specific allergic reaction with the endotoxin of the Bordet-Gengou bacillus. No reliable results were obtained. Both control and patient, with the exception of a few infants, were positive.

An interesting contribution to the pathologic anatomy of whooping cough was made by Mallory and Horner.[78] They found that the cilia of the epithelial cells lining the trachea, bronchi, and possibly the nose were, in the specimens examined, covered with a thick layer of minute bacilli, and believe that the location of the organism is apparently characteristic of the disease and that the action seems to be partly mechanical, producing inhibition of the ciliary movements and of the cellular secretions. The blood changes have again been studied by Schneider,[79] and they are in the main confirmatory of previous workers. His results may be summarized briefly by stating that there is a leukocytosis up to 80,000, the average being 27,000. The mononuclears are relatively increased during the first four weeks, 86 per cent. being the highest and 60 per cent. the average. No prognostic conclusions can be drawn from the blood picture.

Clinic and Complement.—That the notion regarding pertussis, supported by Czerny, who overemphasized the neurotic element, a stand which he has recently disavowed, should find some adherents is not surprising. Dobelli[80] took up this view and was vigorously combated by Feer.[81] Feer admits the psychic element, but believes that it is possible that Czerny was deceived by pertussis-like cough of tuberculosis or that occasionally following pneumonia. The association of pertussis and spasmophilia has been the subject of several communications. Wernstedt[82] tells of an epidemic in which the patients showed increased irritability of the nerves, but no evidence of the presence of specific organisms. Erlanger[83] denies a necessary association between the two conditions.

74. Bacher and Metchnikoff: Centralbl. f. Bakteriol., Orig., 1912, lxi, 218.
75. Bordet: Centralbl. f. Bakteriol., Orig., 1912, lxvi, 236.
76. Netter and Weill: Compt. rend. Soc. de biol., 1913, lxxiv, 236.
77. Neurath, R.: Med. Klin., Berlin, 1914, x, 1619.
78. Mallory, F. B., and Horner, A. C.: Jour. Med. Research, 1912, xxvii, 115.
79. Schneider: München. med. Wchnschr., 1914, lxi, 303.
80. Dobelli, E.: Cor.-Bl. f. schweiz. Aerzte, 1912, Nos. 4 and 23.
81. Feer, E.: Cor.-Bl. f. schweiz. Aerzte, 1912, No. 6.
82. Wernstedt, W.: Hygiea, Stockholm, September, 1912; abstr., München. med. Wchnschr., 1912, lix, 605.
83. Erlanger, B.: Monatschr. f. Kinderh., xii, No. 8.

A number of interesting complications and sequelae are again reported. Roedelius[84] has seen a case of optic atrophy, the seventh on record. He believes this to be due to neural infections as well as to the mechanical influences. Sylvester[85] reports eight patients with cerebral complications, of whom seven died. In two, micro-organisms were demonstrated in the spinal fluid. Weigert[86] saw a meningocele develop in an infant after three weeks of coughing. Later, as the fontanels grew smaller, the tumor disappeared. No permanent injury of the brain was demonstrable. Two months following a severe pertussis polydipsia developed in an 8-year-old patient of von Starch.[87] The diabetes mellitus which was diagnosed was of slight severity.

Vaccine Treatment.—The vaccine treatment of whooping cough has been quite frequently reported. Ladd[88] reports eight patients, of whom three were infants. From 40,000,000 to 50,000,000 bacteria were given. The average duration of the disease was eight weeks. The author draws no definite conclusions as to the beneficial results produced, but feels that the severity of the paroxysms was diminished. Zahorsky[89] reports favorably of his experience. He attributes to the vaccine a certain immunizing power. Nicolle and Connor[90] treated 104 patients and saw fifty-seven cured, thirty-eight improved, while twenty-five were uninfluenced. Bamberger[91] had six cases in which he gave 21,000,000 bacteria every day for from five to fifteen days. This author believes that both the symptoms and severity of the disease were abated and that fewer complications were noted. According to Wilson,[92] whenever a systemic reaction was produced by the vaccine an improvement followed. In his twenty-three cases he used a total of 60,000,000 to 80,000,000 bacteria and felt that a distinct benefit was produced. Sill[93] has a series in which the patients' ages range from six months to three years. In the patients earliest seen the improvement was the most marked. Individual doses of from 2,000,000 to 6,000,000 were given, but improvement was frequently not seen until three injections had been given. In one case he gave a total of 220,000,000 bacteria, at the rate of 40,000,000 every second day. Two exposed patients had weekly injections of 20,000,000 bacteria and did not contract the disease. Scott[94] also was satisfied with the vaccine

84. Roedelius, E.: Arch. f. Kinderh., 1913, lxii, 161.
85. Sylvester, P. H.: Boston Med. and Surg. Jour., 1914, clxx, 406.
86. Weigert, R.: Monatschr. f. Kinderh., 1914, xiii, 139.
87. Von Starch, W.: München. med. Wchnschr., 1912, lix, 1317.
88. Ladd, M.: Arch. Pediat., 1912, xxix, 581.
89. Zahorsky, J.: Interstate Med. Jour., 1912, xix, 844.
90. Nicolle and Connor: Compt. rend. Acad. d. sc., 1913, No. 24, p. 1849.
91. Bamberger, A.: Am. Jour. Dis. Child., 1913, v, 33.
92. Wilson, S. M.: New York Med. Jour., 1913, xcvii, 823.
93. Sill, E. M.: Am. Jour. Dis. Child., 1913, v, 379.
94. Scott, G. D.: New York Med. Jour., xcvii, 176.

treatment, in that a distinct ameliorating influence on the symptoms was found. Luttinger[95] used the vaccine in severe cases in which medicine was of no avail, and in ten of these cases was able to diminish the severity of the paroxysms as well as to shorten the duration of the disease. He believes that he was successful in immunizing against the disease one exposed patient by the use of 50,000,000 bacteria. He prefers the subcutaneous injection. His highest total dose was 150,000,000. One of the most interesting contributions to our knowledge of the use of vaccines comes from Hess,[96] who describes his experience in an orphan asylum of 357 inmates, the patients varying in age from a few days to 6 years. The vaccine was used by him chiefly for prophylactic purposes, although it was also used in treatment. Of 240 patients who were vaccinated with from 100,000,000 to 2,000,000,000 bacteria, twenty, or 8.3 per cent., developed the disease. Of eighty who were definitely exposed, or, to put it in its most unfavorable light, of 130 who were not vaccinated, fifty-nine, or 22 per cent., developed the disease. If the degree of exposure in the two groups of cases was at all comparable, the results are surely most striking. This observer has less favorable statements to make as to the therapeutic efficiency of the vaccine, in that he did not even observe a distinctly beneficial influence on the symptoms. Hartshorn and Moeller[97] found that a certain number of patients improve with commercial vaccine, others did not. They urge the continuation of its use only when a quick and distinct benefit is found. Graham[98] sums up his experiences by stating that about three fourths of the patients are symptomatically benefited. He also ascribes a certain prophylactic value to the vaccine.

It seems probable that any conclusions as to the efficiency of the vaccine treatment of pertussis must be guarded. Knowing the numerous remedies suggested in the past, enthusiastically acclaimed and as quickly dropped from our armamentarium, one wonders whether the vaccine will have the same fate. The reports seem to show, with few exceptions, an influence on the symptoms. Whether this benefit is in the eyes of the observer or is a real one only the future can tell. The further use of the vaccine seems, however, to be definitely indicated. Patients should be treated early and vigorously, but this treatment should be discontinued if beneficial effects are not obtained. While vaccine therapy is still in the experimental stage, still more is this true with regard to the use of the vaccine as a prophylactic. No

95. Luttinger, P.: Med. Rec., New York, 1913, lxxxiv, 1125.
96. Hess, A. F.: Jour. Am. Med. Assn., 1914, lxiii, 1007.
97. Hartshorn, W. M., and Moeller, H. N.: Arch. Pediat., 1914, xxxi, 587.
98. Graham: Arch. Pediat., 1914, xxxi, 578.

harmful results have been reported, however, and there seems no reason why further investigations should not be carried out.

Miscellaneous Treatment.—Popper[99] urges suggestive treatment with the faradic treatment in the later stages of the disease. Ochsenius[100] favors local treatment of the pharynx with 2 per cent. silver nitrate. This also has a psychic effect. Rusca[101] reports an interesting case in which a little patient with pertussis was operated on for a complicating appendicitis. The pain produced by coughing made the child exert its will to control the paroxysms. This emphasizes the psychic element of the disease.

DIPHTHERIA

Statistics and Epidemiology.—The great interest shown in diphtheria in recent years is due undoubtedly to the fact that although we have an effective means of diagnosis and treatment, still the morbidity rate and mortality has not tended to show so great a diminution as might be expected. Abel,[102] speaking of conditions in Germany from 1892 to 1898, shows that the total number of deaths from diphtheria in one year is greater than those from scarlet fever. The city mortality is higher than that of the country. He urges more intensive and more systematic cultures in order to control this condition. Braun[103] also emphasizes this fact in regard to the city of Berlin. Von Drigalski[104] shows that by systematic culturing and isolation it was possible to rid a population of nearly 200,000 of much of its diphtheria. In this connection reference should be made to the excellent treatise by von Behring[105] on the subject of the control of contagious diseases. Seligman and Schloss[106] describe in detail their carefully controlled attempts to weed out diphtheria in several schools and institutions. Throughout the report they emphasize the necessity of systematic culturing, as well as the desirability of routine cultures, before patients are admitted. The significance of snuffles in infants is also recognized, although they fail to give sufficient mention to this same symptom in older children. Details relating their experiences with treatment, etc., are given.

Teague[107] reports some experiments done to show how far droplet infection plays a part in the spread of the disease. He found that in

99. Popper, E.: Med. Klin., 1913, No. 26.
100. Ochsenius: Therap. d. Gegenw., 1913, liv, 502.
101. Rusca, F.: Cor.-Bl. f. schweiz. Aerzte, 1914, No. 19.
102. Abel, R.: Centralbl. f. Bakteriol., 1912, lxiv, 229.
103. Braun, W.: Deutsch. med. Wchnschr., 1912, xxxix, 255.
104. Von Drigalski: Berl. klin. Wchnschr., 1912, xlix, 1792.
105. Von Behring: Einführung in die Lehre von der Bekämpfung der Infektionskrankheiten.
106. Seligman, E., and Schloss, E.: Ztschr. f. Kinderh., 1912, iv, 451.
107. Teague, O.: Jour. Infect. Dis., 1913, xii, 398.

talking or coughing only small numbers of droplets are emitted and these but a few inches from the mouth, thus forcing the conclusion that contact infection direct or indirect, is, as in other contagious diseases, the chief method of propagation. That one attack of diphtheria does not confer a lasting immunity is shown by Montefusco,[108] who saw a patient with three clinical attacks in eight months. Reiche[109] writes of his experience in a recent severe diphtheria epidemic in Hamburg, in which he encountered 344 patients who had previously had diphtheria. Of these, 119 had never received antitoxin.

Carriers and Contacts.—Von Hoff[110] concludes that in a large number of cases diphtheria bacilli will persist up to five months after the disappearance of the clinical symptoms, even though the cultures are negative. After this they tend to diminish. Brückner[111] and others bring out a most interesting fact, namely, that at certain times of the year at Dresden it seems that the percentage of bacillus carriers undergoes an enormous but not to be explained increase, up to 48 per cent. of examined cases. These cultures are found in a large number of children who are not clinically ill. It is not stated, however, whether this increase is connected with the increase of the number of clinical cases of diphtheria and whether these patients are not really contacts. This brings up, of course, the well-known difficulty of determining the significance of the culture morphologically positive. Van Biemsdyk[112] found among thirty-three children, nineteen of whom had just had diphtheria, organisms resembling Klebs-Loeffler bacillus in twenty-four instances. Of these, but two were virulent. In a region free from diphtheria for ten years, in 50 per cent. of children examined the same organisms were found. His criteria of virulence were the formation of acid and agglutination in a dilution of at least 1 to 500. Riebold[113] saw an epidemic produced in a children's colony by a carrier. Delyannis[114] also emphasizes the importance of isolation and treatment of carriers. In three villages endemic diphtheria was not controlled until the carriers had been recognized. Arms and Whitney[115] also emphasize the rôle of contact in the spread of diphtheria.

Pathologic Anatomy and Physiology.—Abramow[116] studied the hypophysis in experimental diphtheria and believes that there is an early hyperstimulation and hypersecretion with resulting exhaustion.

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108. Montefusco, A.: Gazz. d. osp., March 16, 1913, xxxiv, No. 32.
109. Reiche, F.: Med. Klin., 1913, ix, 1668.
110. Von Hoff, G.: Monatschr. f. Kinderh., 1914, xiii, 133.
111. Brückner: Abstr., München. med. Wchnschr., 1913, lx, 554, 609.
112. Van Biemsdyk, J. M.: Nederl. Tijdschr. v. Geneesk., 1914, p. 1066.
113. Riebold, G.: München. med. Wchnschr., 1914, lxi, 923.
114. Delyannis, K.: Wien. klin. Wchnschr., 1913, xxvi, 1389.
115. Arms and Whitney: Am. Jour. Pub. Health, 1912, No. 10, 799.
116. Abramow, S.: Virchows Arch. f. path. Anat., 1914, ccxiv, 408.

It is interesting to note, however, that the first changes appear in the adrenal. The author, however, does not definitely state that there is an interrelation between these two glands. Kreutsfeldt and Koch[117] also find the pars intermedia of the hypophysis markedly affected, there being in guinea-pigs a diminution in size with granular cystic degeneration. Wildebrand[118] examined the hypophysis in fatal cases of diphtheria in children and finds again distinct degenerative changes in the pars intermedia. He emphasizes the therapeutic value of pituitrin in these severe cases of diphtheria. Moltschanoff[119] again emphasizes the marked change in the adrenal glands and sees in this pathology the justification for the great potency of epinephrin in cardiac collapse.

Involvement of the heart in diphtheria is commented on by Rohmer.[120] In two cases, although heart block was demonstrated by the electrocardiogram at autopsy, the His bundle was found to be relatively unaffected. Tanaka,[121] however, finds a uniform diffuse degeneration of the auriculoventricular bundle, although in one case of severe arrhythmia this muscle filament showed no change. Several other communications have appeared on this subject. Wilson[122] in his résumé refers to the chief of these.

While it has been commonly assumed that the vasomotor center is greatly affected and is believed to be the cause of the circulatory collapse in diphtheria intoxication, Porter and Pratt[123] in their animal experiments have been unable to find evidence to bear out this statement. The earlier views have been probably due to faulty interpretation of experiments. This is one other fact which tends to indicate that suprarenal failure plays an almost sole part in this condition. The finer mechanism of this is shown by McCallum[124] in the isolated heart of an animal, with an artificial circulation containing diphtheria toxin. He shows that if there is sufficient pressure in the coronary artery, the heart will still beat for hours. Leede[125] examined the blood in fatal cases during an epidemic of unusual severity. Out of 256 cases he found the streptococcus in 205, the pneumococcus in twenty-three, the Klebs-Loeffler baccillus in nine, and the latter in conjunction with streptococcus in four. Liedke and Volckel,[126] however, in seven

117. Kreutsfeldt, G., and Koch, R.: Virchows Arch. f. path. Anat., 1913, ccxiii, 123.
118. Willebrand: Zentralbl. f. d. ges. inn. Med. u. d. Grenzgeb., 1912, iii, 132.
119. Moltschanoff, W.: Jahrb. f. Kinderh., 1912, Supplement 200.
120. Rohmer, P.: Jahrb. f. Kinderh., 1912, lxxvi, p. 391.
121. Tanaka: Virchows Arch. f. path. Anat., 1912, ccvii, 113.
122. Wilson, F. N.: Am. Jour. Dis. Child., 1915, x, 376.
123. Porter, W. T., and Pratt, J. H.: Am. Jour. Physiol., 1914, xxxiii, 431.
124. McCallum, W. G.: Am. Jour. Med. Sc., 1914, cxlvii, 37.
125. Leede, W. H.: Ztschr. f. klin. Med., 1913, lxxvii, 297.
126. Liedke and Volckel: Deutsch. med. Wchnschr., 1914, xl, 594.

fatal cases, found diphtheria bacilli in the heart, lungs, spleen, kidneys and in the bone marrow. Reye,[127] in sixty-seven cases, found bacteria in the lungs fifty-six times. Of these, the diphtheria bacillus was in pure culture but six times; twenty-seven times it was associated with streptococci and in twenty-three cases with other micro-organisms.

Bacteriology.—Unending attempts are being made to simplify the interpretations of the laboratory findings in diphtheria and to bring them into harmony with the clinic. The fact that the mere morphology gives no positive information and the fact that not only in the culture but also in the throat the organisms of diphtheria tend to undergo involution, though apparently retaining the power to again become virulent, make the problem almost hopelessly difficult. Thiele and Embleton[128] report that they have been able to transmute a characteristic Hoffman diphtheroid into a virulent organism with the typical morphology of the diphtheria bacillus, capable of producing pathologic changes in a guinea-pig. The significance of this is at once apparent. If verified, it would indicate that the involution types of organisms found in the respiratory tract of the patient so many months after the disappearance of clinical symptoms are still capable of producing infection. The opposite has been accomplished by Römer.[129] He transforms the virulent into an avirulent modification by passage through guinea-pigs. Meunier still adheres to the commonly accepted views that the polar body organisms and the barred and solid types are the only ones to be feared. Baerthlein[131] found that in progressive cultures the diphtheria bacilli lost their virulence, and with this is associated a change in the form and appearance of the colony produced. Kolmer,[132] from a large series of cultures, concludes that only the granular type, using the classification of Westbrooke, are virulent. The barred types are of doubtful significance, while the small forms may be excluded, unless small polar granules are found, when they are to be regarded as positive. Kolmer,[133] using the complement fixation reaction as a basis for classifying the diphtheria-like bacilli, shows that all of them are related and that the true Hoffmann bacillus is probably an example of mutation.

There is no relation between the occurrence or degree of complement fixation and the antitoxin strength of the immune serums. This again brings up the fact, commonly overlooked, that not only is there

127. Reye, E.: München. med. Wchnschr., Oct. 29, 1912, lix, 2383.
128. Thiele and Embleton: Ztschr. f. Immunitatsforsch. u. exper. Therap., 1913, xix, 643, 666.
129. Römer, P. H.: Berl. klin. Wchnschr., 1914, li, 503.
131. Baerthlein, K.: Berl. klin. Wchnschr., 1913, l, No. 22.
132. Kolmer, J. A.: Jour. Infect. Dis., 1912, xi, 56.
133. Kolmer, J. A.: Jour. Infect. Dis., 1912, xi, 44.

an antitoxic, but also an antibacterial, immunity developed. Menard,[134] cultivating diphtheria bacilli on serum in contact with antitoxin, found them unaffected; they seemed, however, to lose their power of producing toxin. Lavari[135] in this connection has been able to find by means of the complement fixation test that there is an antibacterial amboceptor to be found in antitoxin. No conclusions are drawn as to its significance. Townsend[136] reports the finding of virulent pseudodiphtheria bacilli in the urinary tract. Kolmer[137] in forty cases made 100 cultures from the penis, and finds diphtheroid bacilli which, however, he states to be avirulent.

Cultural Methods.—Conradi and Troch[138] describe a new medium for elective culture of diphtheria bacilli. This consists in ordinary beef serum in which is incorporated a small percentage of sodium tellurate and of calcium malate. The diphtheria bacilli are first grown on ordinary Loeffler's serum for three hours and are then transferred to plates of the new mixture. The diphtheria bacilli colonies are supposed to reduce the tellurate, a black colony resulting. Other micro-organisms are stated not to do this. Calcium malate is supposed, moreover, to retard the growth of these other organisms. Several investigators have used this plan and their reports are far from enthusiastic. Hanau[139] sees no proportionate advantage over the older method. Klunker[140] is of the same opinion. Schurmann and Hajos,[141] however, used the Conradi-Troch plates and omitted the simple serum altogether. They found a larger number of positive cultures as well as a simplification of the picking out of colonies. Wagner[142] found no more positive results, but found it easier to locate the organisms. Markl and Pollak[143] speak well of this new medium.

Another improvement is suggested by von Drigalski and Bierast.[144] They add 3 per cent. sterile ox bile to Loeffler's glucose bouillon serum. Voelckel,[145] Schulz,[146] and Grundman[147] are not favorably impressed with their experiences. Conradi[148] has an ingenious technic for sepa-

134. Menard, P.: Presse méd., 1913, xxi, 636.
135. Lavari: Ann. d. Ist. Maragliano p. la cura d. tuberc., 1913, vii, No. 2.
136. Townsend, W. W.: Jour. Am. Med. Assn., 1913, lxi, 1605.
137. Kolmer, J. A.: Arch. Pediat., 1912, xxix, 94.
138. Conradi and Troch: München. med. Wchnschr., 1912, lix, 1652.
139. Hanau: Centralbl. f. Bakteriol., 1913, lxxii, 245.
140. Klunker: München. med. Wchnschr., 1913, lx, 1025.
141. Schurmann, W., and Hajos, E.: Deutsch. med. Wchnschr., 1913, xxxix, 786.
142. Wagner, G.: München. med. Wchnschr., 1913, lx, 457.
143. Markl and Pollak: Wien. klin. Wchnschr., 1913, xxvi, 1617.
144. Von Drigalski, W., and Bierast: Deutsch. med. Wchnschr., 1913, xxxix, 1327.
145. Voelckel, E.: München. med. Wchnschr., 1913, lx, 883.
146. Schulz, F. C. R.: Deutsch. med. Wchnschr., 1913, xxxix, 2195.
147. Grundmann: Berl. klin. Wchnschr., 1913, l, 2287.
148. Conradi, P.: München. med. Wchnschr., 1913, lx, 1073.

rating the diphtheria bacilli from other micro-organisms, based on the fact that if a mixed culture be shaken up in a test tube containing salt solution and oil, the diphtheria bacilli will be taken up by the oil, whereas the rest of the organisms go into the salt solution. Cotton swabs surrounded by filter paper and moistened with ligroin are dipped into the oil later, the oil passing through the paper into the cotton and the bacteria remaining on the filter paper. Af Heurlin[149] attempts to differentiate by cultural methods the true and the false diphtheria bacilli. This is based on the capacity which the true diphtheria bacilli have of developing without oxygen. Consequently, in deep stabs into alkaline phenolphthalein glucose agar, the true bacilli will be toward the bottom. On blood glucose phenolphthalein agar it is found that pseudodiphtheria bacilli do not produce hemolysis.

Immunology.—Interesting steps in advance are found in the introduction of the intradermal application of diphtheria toxin for clinical purposes by Schick and a like clinical application by von Behring of a suggestion made first by Theobald Smith, namely, that mixtures of toxin and antitoxin be used to actively immunize against diphtheria. The first full communication of Schick[150] has to do with the application of the so-called Römer test and the first observations were done with the blood serum of a diphtheria patient to determine the toxin content.

In another communication he[151] finds that local hypersensitization does not result, even though the tests be frequently repeated. He also used this method[152] as a means of determining the amount of diphtheria antitoxin necessary to neutralize circulating toxin and found that by giving as little as 500 units per kilogram of body weight (250 units per pound) in 91 per cent. of all cases the toxin reaction could be prevented. In other words, this amount of antitoxin was sufficient to neutralize not only the circulating toxin, but also that amount in addition which was introduced for the test. No retroactive power of the serum could be made out—another confirmation of the importance of early treatment. Prophylactic injections were given only to those patients who had a positive toxin test. He[153] suggests that if the intracutaneous tests are negative, there are sufficient protective bodies in the patient's serum, and he also concludes that there is an immunity in these cases. As to whether the diphtheria bacillus might not gain a hold in the mucous membrane in spite of this immunity is not discussed. The strength of

149. Af Heurlin, M.: München. med. Wchnschr., 1914, lxi, 703.
150. Schick, B., and Michiels, J.: Ztschr. f. Kinderh., 1912, v, 255.
151. Schick, B.: Centralbl. f. Bakteriol., 1912, lxvi, 121.
152. Schick, B.: Wien. klin. Wchnschr., 1914, xxvii, 1966.
153. Schick, B.: München. med. Wchnschr., 1913, lx, 2608.

the toxin suggested for this test is such that 0.1 c.c. is equivalent to $\frac{1}{50}$ of the lethal dose for a guinea-pig which weighs about 250 gm.

Park, Zingher and Serota[154] have tried out this reaction in 700 cases of scarlet fever. Fifty-seven per cent. (400 cases) gave negative reaction and developed no diphtheria, although the patients did become carriers. Using this reaction, they also found that the intravenous administration of serum was more effective than the subcutaneous or intramuscular. Kleinschmidt[155] found that of eighteen infants, sixteen showed no antitoxin in the blood. The two patients in whom antitoxin was found were in an institution where they may have been exposed. Of sixteen infants who were bacillus carriers, antitoxin was found in the blood of ten, as much as 2.5 units per cubic centimeter being determined. Otto[156] found that the percentage of antitoxin in adults is greater in those who are frequently exposed to diphtheria, as in a hospital. Carriers and excretors of the bacilli also showed a high content. An acute infection gives only a moderate immunity, whereas a chronic infection is necessary for this purpose. Larval infections, without symptoms, are especially potent. Schütz[157] also in a series of cases finds that the Schick test gives a definite clue as to the susceptibility of the patients. Hahn[158] also, using the method of Römer, shows that attendants in diphtheria wards and others frequently exposed have the highest antitoxin content of the blood. Kassowitz and Gröer[159] show that the immunity of the new-born, which exists in 80 to 90 per cent. of all cases, depends on the antitoxin derived from the mother's blood. Beyer[160] found that antitoxin was found in the blood of every patient who had been injected, from one-half to four-fifths of the total quantity being present. On the fifth and the sixth days from one-fifth to three-tenths were still present. In from two to three weeks only from five- to six-hundredths could be demonstrated. In certain instances a larger amount was found than would be theoretically expected. Harriehausen and Wirth[161] found toxin in the blood of patients with diphtheria, using the Römer method. Less than 0.1 c.c. of serum was sufficient to produce necrosis and, indeed, in one fatal case 0.04 c.c. caused a very severe necrosis in twelve hours. In ten cases of postdiphtheritic paralysis toxin was found five times.

Theobald Smith in 1903 found that a mixture of diphtheria toxin and antitoxin, in which the former was in slight excess, caused a pro-

154. Park, Zingher, and Serota: Arch. Pediat., 1914, xxxi, 481.
155. Kleinschmidt, H.: Jahrb. f. Kinderh., 1913, lxxviii, 442.
156. Otto, R.: Deutsch. med. Wchnschr., 1914, xl, 542.
157. Schütz: München. med. Wchnschr., 1913, lx, 2608.
158. Hahn: Deutsch. med. Wchnschr., 1912, xxxviii, 1366.
159. Kassowitz and Gröer: Abstr., Jahrb. f. Kinderh., 1913, lxxviii, 609.
160. Beyer, W.: Deutsch. med. Wchnschr., 1912, xxxviii, 2353.
161. Harriehausen and Wirth: Ztschr. f. Kinderh., 1913, vii, 132.

duction of a large amount of antitoxin in the blood without producing serious symptoms and suggested then that this method might be used to advantage in children. Von Behring[162] was the first to apply this on a large scale and sent out mixtures for use, determining that the observations should be made with the greatest exactness possible by means of regular examination of the content of the blood of the children immunized. His program is a model of thoroughness. He states in his first communication that the presence of 0.1 of a unit per cubic centimeter of blood was sufficient to protect individuals during an epidemic; with the injection of 100 units into a child the antitoxin disappears in 20 days after reaching 0.025 per c.c. If a homologous serum is used, the passive immunization endures a considerably longer time. He notes that the assumption of the permanent binding of toxin and antitoxin in vitro is a false one and also that the proportion of toxin and antitoxin which will produce symptoms varies with the different species. The human animal is not sensitive at birth, but becomes so after it has been exposed to infections, bacillus carriers, for example, being especially sensitive and producing antitoxin easily. He made a further observation, which requires confirmation, however, that those treated with this new mixture, which will hereafter be referred to as T. A., did not harbor the diphtheria bacilli even though exposed. The experimental work, which is best seen in the original, as, for example, in the article by Viereck,[163] contains many interesting observations. He shows among other things that the adult is 100 times more sensitive, per kilogram of body weight, than is an infant. Zangemeister[164] also finds this lack of susceptibility in the new-born and in those not infected. The method of administration is described by Schreiber.[165] About 0.1 c.c. of the mixtures, of which there are several, is used at intervals of from three to five days and is given as often as three times. Its effect is noted in from twenty-three to twenty-five days. The lowest serum content produced per cubic centimeter was 0.75, the highest 1, although by repeated injections (four to seven), as much as from 10 to 75 units per cubic centimeter was obtained. The author maintains that there must be from 0.04 to 0.1 per cubic centimeter for effective protection. He found four failures in twenty-one cases.

Kleinschmidt and Viereck[166] prefer the intracutaneous rather than the subcutaneous method of administration. Not only is there heightened immunizing power, but there is an added advantage in that the susceptibility of the individual is indicated by the reaction following the

162. Von Behring: Deutsch. med. Wchnschr., 1913, xxxix, 873.
163. Viereck: Deutsch. med. Wchnschr., 1913, xxxix, 978.
164. Zangemeister, W.: Deutsch. med. Wchnschr., 1913, xxxix, 977.
165. Schreiber, E.: Deutsch. med. Wchnschr., 1913, xxxix, 928.
166. Kleinschmidt and Viereck: Deutsch. med. Wchnschr., 1913, xxxix, 1977.

injection. For example, there may be no more than simple redness produced in some cases, while in others a more general reaction, with fever, malaise, headache and swelling of the lymph glands follows. If the second injection produces a local reaction with distinct redness and swelling, they expect to find about 0.5 units of antitoxin produced per cubic centimeter of blood. Kissling[167] immunized 310 children by this method and of the 111 children who received two prophylactic injections, none contracted diphtheria. Of the 119 who received but one, eight developed the disease. Von Behring and Hagemann[168] also used the intracutaneous method, using 0.1 c.c. of total solution, but they were not of the opinion that the degree of local reaction was an indication of the amount of antitoxin formed. Bauer[169] was unable to free ten carriers of their bacilli by this method. Park, Zingher and Serota[170] used the Schick test to determine whether the active immunization was indicated and found that two thirds did not require it. They determined that the active immunity might not develop until late and when produced lasted from one to two years. Kohn and Sommers[171] used this method in five epidemics, 633 cases in all being immunized. They also used the intracutaneous method. Of these patients only two developed the disease and that in a mild form.

Schrieber[172] reports a total of 700 patients treated, of whom but twelve developed diphtheria. Blacher[173] has analyzed the various types of gallop rhythm. His most important conclusion is that an increase in peripheral resistance is one of the causes, so that it is not necessarily an index of the myocardial change. He assumes that the heart in diphtheria is very sensitive to all stimuli—nervous, mechanical, etc.

Diagnosis and Clinical Findings.—That there may be some difficulty in the diagnosis of diphtheria is shown in the communication of Charlier,[174] who states that phlegmonous angina and malignant diphtheria are almost indistinguishable and if the possibility of the latter disease is not borne in mind and no cultures taken, unsuitable treatment may be instituted. The association of Vincent's angina and diphtheria, or the presence of diphtheria bacilli in cases which are clinically Vincent's angina, is described by Reiche.[175] The author, however, does not discuss the question of serum therapy. Weill[176] summarizes the vari-

167. Kissling: Deutsch. med. Wchnschr., 1913, xxxix, 2500.
168. Von Behring and Hagemann: Berl. klin. Wchnschr., 1914, li, 917.
169. Bauer, J.: Deutsch. med. Wchnschr., 1914, xl, 582.
170. Park, Zingher and Serota: Jour. Am. Med. Assn., 1914, lxiii, 859.
171. Kohn and Sommers: Deutsch. med. Wchnschr., 1914, xl, 13.
172. Schreiber: Therap. d. Gegenw., 1914, lv, 98.
173. Blacher, W.: Jahrb. f. Kinderh., 1914, lxxix.
174. Charlier, G.: Hygiea, Stockholm, lxxv, No. 6; abstr., Jour. Am. Med. Assn., 1913, lxi, 1084.
175. Reiche, F.: Med. Klin., 1914, x, 1381.
176. Weill, E.: Patholog. Infantile, 1913, x, 101.

ous faucial manifestations of diphtheria and emphasizes especially the perforating, ulcerating, anginal form, which is of a very severe character and which has a tendency to form ulcers in the soft palate, in the gums and other portions of the buccal mucous membrane. Various secondary invaders are found on culture. Lind[177] emphasizes the fact that pharyngeal diphtheria may run a mild course without membrane formation, the diagnosis not being made unless cultures are taken. He fails to state whether or not nasal diphtheria, so commonly associated with this type of infection, was present.

The need of emphasizing the significance and frequency of nasal diphtheria is shown in numerous articles. Moss[178] calls attention to it from the point of view that it is a neglected source of infection in the public schools. Conradi[179] describes the prevalence of nasal diphtheria in infants with nutritional disturbances and shows that serum therapy is without effect. Von Bokay[180] reports two cases of diphtheria of the gums in infants in whom the initial infection was in the nasal tract.

Forbes and Newsholme[181] discuss the possible association of membranous rhinitis and diphtheria. For therapy they prefer an autogenous vaccine composed of streptococci and Klebs-Loeffler bacilli. They did not use serum. David[182] assumes that he has seen a case of acute primary diphtheritic pneumonia. A secondary rise in temperature following the crisis led to death. At necropsy tracheal diphtheria was made out and the diphtheria bacilli cultivated in almost pure culture from the lungs. Tylecote[183] reports a case of diphtheria of the stomach with fatal outcome. Cargin[184] reports a case of membranous enteritis, diphtheritic membranes being passed during the ten days of the illness. Pollak[185] observed a case of diphtheritic sepsis following an infection which resulted from the piercing of the ears in an infant. Kleinschmidt[186] is able to corroborate the statement of Bingel that the intracutaneous injection of toxin produces a very great response in the formation of antitoxin. In the case of anal diphtheria Blühdorn[187] reports epidemics in which the cases were of unusual severity, so that from 20,000 to 30,000 units of antitoxin were insufficient to prevent postdiphtheritic palsies.

177. Lind, S. C.: Jour. Am. Med. Assn., 1913, lx, 1412.
178. Moss, E.: New Orleans Med. and Surg. Jour., 1913, lxv, 703.
179. Conradi, E.: München. med. Wchnschr., 1913, lx, 512.
180. Von Bokay, Z.: Ztschr. f. Kinderh., 1914, xi, 191.
181. Forbes and Newsholme: Lancet, London, 1912, No. 4614, p. 292.
182. David, O.: München. med. Wchnschr., 1913, lx, 2431.
183. Tylecote, F. E.: Brit. Jour. Child. Dis., 1913, x, 211.
184. Cargin, H. M.: Lancet, London, 1913, No. 175, p. 23.
185. Pollak, R.: Wien. klin. Wchnschr., xxvi, 1306.
186. Kleinschmidt: München. med. Wchnschr., 1913, lx, 1477.
187. Blühdorn, K.: München. med. Wchnschr., 1912, lix, 1266.

Diphtheria bacilli in the urine are found by numerous observers. Koch[188] took 111 samples from twenty-six patients and found characteristic virulent micro-organisms four times in the urine of two patients. They were found, however, only in the early stages in severe cases in which the patients died with symptoms of cardiovascular failure. Conradi and Bierast[189] found in 155 cases that fifty-four excreted diphtheria bacilli. Beyer[190] also has high positive results, finding them even in cases where the patients harbor the bacilli in the tonsils. Freifeld[191] reports a case of secondary cystitis in which the diphtheria bacilli were present for many months, treatment being without effect.

Complications.—Benesi[192] describes three types of diphtheritic otitis; (*a*) primary diphtheria of the ear; (*b*) secondary diphtheria of the ear; (*c*) diphtheritic otitis associated with general infection. Jervis[193] reports a case of pulmonary abscess. Beyer[194] saw a case of fetid diphtheritic bronchitis with recovery. Schmidt[195] saw a case of bronchiectasis in which diphtheria bacilli were present in the sputum for two years. Stewart[196] reports a case of pulmonary embolism in which the initial attack, which was mild, became rapidly severe. Leede[197] describes four cases of postdiphtheritic hemiplegia. Reiche[198] shows that in eight cases of meningitis the infecting microorganism was never the diphtheria bacillus, being either the meningococcus, B. Coli, streptococcus, pneumococcus or staphylococcus. Dynkin[199] describes the necropsy findings in a case of cerebral involvement with aphasia, in which widespread softening was noted. Wolff[200] saw a case of postdiphtheritic facial palsy following nasal diphtheria. According to Schuster,[201] certain strains of diphtheria bacilli may excrete a neurotropic toxin. Thus, three members of the family suffered with postdiphtheritic paralysis.

Therapy.—The intravenous therapy first suggested by von Behring in 1901 has been extensively practiced of late years, but little critical work has appeared with regard to its possible clinical advantage. Beyer[202] tried it in twenty-six cases and obtained the impression that

188. Koch, R.: Deutsch. med. Wchnschr., 1912, xxxviii, 2358.
189. Conradi and Bierast: Deutsch. med. Wchnschr., 1912, xxxviii, 1580.
190. Beyer, W.: München. med. Wchnschr., 1913, lx, 240.
191. Freifeld, E.: Berl. klin. Wchnschr., 1913, l, 1761.
192. Benesi, O.: Wien. klin. Wchnschr., 1912, xxv, 1385.
193. Jervis, J. J.: Brit. med. Jour., 1914, i, No. 2781, p. 859.
194. Beyer: München. med. Wchnschr., 1913, lxi, 25.
195. Schmidt: Berl. klin. Wchnschr., 1912, xlix, 2090.
196. Stewart, D.: Lancet, London, 1912, No. 4622, p. 866.
197. Leede, W. H.: Ztschr. f. Kinderh., 1913, viii, 88.
198. Reiche, F.: Ztschr. f. Kinderh., 1914, xi, 452.
199. Dynkin, A. L.: Jahrb. f. Kinderh., 1913, lxxviii, Supplement 267.
200. Wolff, S.: Jahrb. f. Kinderh., lxxvii, No. 2.
201. Schuster, P.: Neurol. Centralbl., 1914.
202. Beyer, W.: München. med. Wchnschr., 1913, lx, 1867.

the membrane disappeared more quickly when a subcutaneous injection was practiced, although its advantage was slight. Alber,[203] on the other hand, is of the opinion that striking results were achieved in thirty-two very severe cases, in which the intravenous administration of serum was combined with intramuscular injections. Of these patients, but two died, even though it was necessary to do five tracheotomies. Fever dropped strikingly in two days at most, and the membrane seemed to come off more quickly. Only one case of serum rash followed. There were, however, eight cases of paralysis of the soft palate, but no general neuroparalysis. Park[204] covers the subject of antitoxin administration and considers it from several aspects. Conclusions drawn from his animal experiments verify the observations of other observers; as, for example, the fact that a heterologous serum disappears from the circulation more rapidly than does a homologous serum. When given subcutaneously the maximum antitoxin content of the blood is not achieved until after forty-eight hours, although it lasts from two to three days. He feels that it is better to give one large dose than several small ones. Intravenous administration of serum is indicated in severe cases, 5,000 units in this way being equivalent to 20,000 subcutaneously. Woody[205] discusses the effect of very large doses of antitoxin on the basis of mortality statistics. The following figures taken from hospital cases are as valuable as data of this kind can be:

Year	Cases	Deaths	Per Cent.	Dosage
1908.....	1426	127	8.55	Very small
1909.....	2153	144	6.69	Large
1910.....	1870	120	6.42	Larger than 1909
1911.....	1895	130	6.86	Smaller than 1909-1910
1912.....	1676	101	6.02	Larger doses

Nemmser[206] urges the use of the Besredka method of giving antitoxin and shows that the danger even with repeated antitoxin administration is very slight. Schibayama[207] tried to avoid anaphylactic phenomena by the rectal administration of antitoxin, but he found that it did not give an appreciable passive immunity. The account of several experiences with the intralumbar administration of serum have appeared. Porak,[208] in a case of severe postdiphtheritic paralysis, gave seven such treatments in as many days, with satisfactory results. Kleinschmidt,[209] on the basis of laboratory experiments as to the firmness of union between toxin and brain tissue and the power of antitoxin to

203. Alber, K.: Jahrb. f. Kinderh., 1914, lxxx, 312.
204. Park, W. H.: Boston Med. and Surg. Jour., 1913, clxvii, 73.
205. Woody, S. G.: Jour. Am. Med. Assn., 1914, lxiii, 861.
206. Nemmser, M.: Deutsch. med. Wchnschr., 1913, xxxix, 740.
207. Schibayama, C.: Deutsch. med. Wchnschr., 1913, xxxix, 738.
208. Porak: Bull. Soc. de pédiat. de Paris, 1912, p. 314.
209. Kleinschmidt, H.: Jahrb. f. Kinderh., 1912, lxxvi, 179.

separate such mixtures, urges this method of treatment, even though the experiments are disputed by Beyer.[210] Bingel[211] interprets the vomiting which occurs in malignant diphtheria five or more days after the onset of the disease (when the local signs in the throat are moderate) as being of cerebral origin. He also gave the serum by injection into the lumbar space. Symptomatic improvement was noted, but the high mortality was not diminished. Weintraud also urges this form of treatment.

Krause and Becher[213] emphasize the fact that the curative action of diphtheria antitoxin does not depend necessarily upon its strength in vitro. There seems to be a variation of the avidity of different antitoxins for toxin.

The use of vaccine or bacterial substances in the treatment has been attempted with varying results. This method has been used chiefly in the case of carriers or in low grades of infections. Hewlett and Nankivell[214] used the method of McFadyen, which consists in the grinding, in the presence of intense cold, of the washed diphtheria bacilli and then passing the material through a Berkefeld filter. Results in active cases are not greater than by the method of serum administration. It is interesting to note that one patient was cured only after a necrotic turbinate in the nose had been removed.

Treatment of Carriers.—Petruschky found success in the treatment of carriers by vaccine made from bacilli killed by chloroform and washed free of toxin. Meyer[216] also had good results, especially in the treatment of nasal diphtheria in infants. Weil[217] reports the results in fifteen cases, in only six of which were they satisfactory. In these, however, the cultures remained permanently negative. He advises the use of large doses, up to 200,000,000.

It seems to me scarcely necessary to quote completely the literature which has appeared dealing with the "overriding" treatment of diphtheria carriers with staphylococcus cultures (Schiötz). Bissell[218] calls attention to some studies that he has made, unfortunately not published in full, which tend to show that the use of the staphylococcus spray may deceive the observer. This investigator finds that the "overriding" does not produce extermination of the bacilli in the fauces, but that in

210. Beyer, W.: Jahrb. f. Kinderh., 1913, lxxvii, 65.
211. Bingel, C.: Deutsch. Arch. f. klin. Med., 1911, civ, 370.
213. Krause and Becher: Deutsch. med. Wchnschr., 1913, xxxix, 1081.
214. Hewlett and Nankivell: Lancet, London, 1912, No. 4638, p. 143.
216. Meyer, F.: Ztschr. f. Kinderh., 1912, ii, 575.
217. Weil, A. L.: Laryngoscope, 1914, xxiv, 804.
218. Bissell, W. G.: Jour. Am. Med. Assn., 1913, lxi, 1393.

the cultures taken the staphylococci tend to overgrow the diphtheria bacilli in the serum tube. De Witt[219] shows that there is no inherent antagonism between the diphtheria bacillus and the staphylococcus in culture. In animal experiments she also found that, as compared with the controls, in 40 per cent. of the cases the bacilli were gotten rid of more readily by this method, whereas, in 60 per cent. the result was the same. Many of the clinical articles which have appeared on this subject give only a small number of cases, without the careful control suggested as above. Rolleston[220] found that there was nothing accomplished from this treatment in nasal cases. Lorenz and Ravenel[221] show, for example, that in one case in their series the patient became a carrier in three months after this treatment and that the reinfection was again "cured" by the use of spray. They also show that in several instances the cultures, which were negative, again became positive. Alden[222] comments on the different by-effects, such as fever, sore throat and edema of the face. He was satisfied with two negative cultures taken two days following the treatment. Ten Broeck[223] uses the thallophytic fungus, *Achlya mascaris,* as a spray.

The fact that the diphtheria bacilli in carriers localize themselves either in the crypts of the tonsils or in the nasal tissues is being recognized more and more as a basis on which efficient treatment of these troublesome cases must be founded. Reference has been made to the work of Hewlett and Nankivell,[214] wherein mention is made of the necessity of removing a necrotic turbinate. Albert,[224] after reviewing the methods, suggests that the crypts be cleaned out and treated with a strong antiseptic solution. Greene[225] removes the tonsils and adenoids in bacillus carriers, preceding the operation with prophylactic doses of serum. Dreyfus,[226] while reporting but one case, brings out a very valuable point. The patient described suffered with polyneuritis, chiefly sensory in character. The infection took place in June, the neuritis developing the month after. At the time of operation the antitoxin content of the blood was 0.10 unit per cubic centimeter. In spite of this, 2,000 units were given as an added precaution. The tonsils were found to contain pus, and the presence of diphtheria bacilli was easily demonstrated. Immediate improvement was noted and a complete recovery obtained after removal of the tonsils.

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219. De Witt: Jour. Infect. Dis., 1912, x, 24.
220. Rolleston, J. D.: Brit. Jour. Child. Dis., 1913, x, 298.
221. Lorenz and Ravenel: Jour. Am. Med. Assn., 1912, lix, 690.
222. Alden, A. M.: Jour. Am. Med. Assn., 1913, lxix, 1876.
223. Ten Broeck, L. L.: Med. Rec., New York, 1914, lxxxv, 49.
224. Albert: Am. Pub. Health Jour., 1913, lxi, 1027.
225. Greene, J. B.: Boston Med. and Surg. Jour., 1913, clxviii, 912.
226. Dreyfus: Med. Klin., 1914, x, 970.

SCARLET FEVER

Epidemiology.—Striking advance has been made in recent years in the study of scarlet fever. As to the nature of the disease, Von Szontagh[227] reviews his earlier experiences and statements and emphasizes his notion, without bringing out definite experimental evidence, that scarlet fever differs from tonsillitis only in the fact that it indicated a peculiar reaction on the part of the body to the infecting microorganism. The circumstantial evidence which he relies on to bear out his very firm conviction is found in the frequency of the so-called idiopathic origin of cases without epidemic, the great variability of the rash, the variation in infectiousness, and the long infectivity of the purulent discharges from the nose and ears. He shows, for example, that the frequency of scarlet fever during the year in Budapest tends to remain at a more constant level throughout the year, than is the case in other diseases, such as measles, in which distinct seasonal variations are found.

The question of the existence of scarlet fever in Japan is discussed in a communication,[228] and while it is not distinctly proved that scarlet fever does not exist, it seems quite certain that the disease is one of very great rarity or, if present, occurs in a form which is either different from the type we are accustomed to see, or is very difficult to recognize. The method of transmission by books is discussed by Nesbit.[229] During an epidemic it seemed quite probable that the books from the public library played no part in the spreading of the disease. Fleas are blamed in the London letter[230] for the transmission of scarlet fever. These parasites in London multiply during late summer and autumn, but are not so prolific in winter. The curve of the incidence of scarlet fever parallels this exactly.

The question of a familial predisposition to scarlet fever and especially to the complicating nephritis is a subject of discussion between Mathies[231] and Bode.[232] Using the statistical method, the former concludes that there is no distinctly peculiar familial disposition, stating that members of the same family need not have the same type of the disease and that there may often be several different streptococci complications in such a group. The latter, using the same method, finds just the reverse. Urszinji[233] believes that in time of epidemics children should be subjected to routine throat gargles with an antiseptic solution.

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227. Von Szontagh: Jahrb. f. Kinderh., 1912, lxxvi, pp. 1 and 654.
228. Jour. Am. Med. Assn., 1913, lix, 669.
229. Nesbit, O. B.: Jour. Am. Med. Assn., 1912, lix, 1526.
230. London Letter: Jour. Am. Med. Assn., 1914, lxii, 1183.
231. Mathies: Jahrb. f. Kinderh., 1913, lxxviii, Supplement, 116.
232. Bode, P.: Jahrb. f. Kinderh., 1914, lxxix, 438.
233. Urszinji, J.: Pest. med.-chir. Presse, 1913, p. 245.

Vaccine prophylaxis is urged by Watters,[234] who uses the method of Gabritschewsky. Three injections of streptococcus vaccine were given at intervals of eight days to nurses who had not yet had scarlet fever. Of the fourteen not injected, five developed the disease; of the twenty-one injected, only one developed the disease. De Biehler,[235] Krukowsky,[236] and Czarkowsky,[237] all used this method and found that of 128 cases only two developed the disease. Keifer and Ferry,[238] in a rather small series also have a favorable impression of the value of this method of prophylaxis. Their vaccine contained both streptococcus and a so-called micrococcus "S." Several injections of about 200,000,000 organisms at intervals of from two to three days served to render efficient protection. Previous to the use of the vaccine a morbidity of 6 per cent. of those exposed was noted. None were affected while the vaccine was used, but the disease again appeared after ceasing to use it. Not only that, but the mortality and frequency of complications is asserted to have been diminished.

The return cases as a source of infection is discussed by Baginsky,[239] after the matter had been brought up as a result of an English law suit. Sexton[240] has observed sixteen return cases in three years and notes that they may occur even if there is no discharge from the eyes, the ears or the respiratory tract. They occur usually in the winter and are believed to be due to coryza developing. Wegmann[241] in thirty-two return cases found that eighteen were of the exudative type, and he believes that these children with their greater susceptibility to infections of the upper respiratory tract are more likely to harbor the infecting organisms. Higgins[242] believes that when the diphtheria bacillus has been present there is a greater tendency to a prolongation of the infectious stage beyond the ordinarily accepted period. An interesting instance of reinfection is reported by Jacobson.[243] In a family of four all of whom had had scarlatina, which had been diagnosed by several physicians, the disease again developed.

Diagnosis.—The differentiation of scarlet fever from infectious erythema has long been known as being of the greatest difficulty. Any method which will be of assistance has been eagerly seized upon. Döhle[244] reports further investigations dealing with leukocytic inclusion

234. Watters, W. H.: Jour. Am. Med. Assn., 1912, lxiii, 546.
235. De Biehler, M.: Arch. de méd. d. enfants, 1914, xvii, 193.
236. Krukowsky: Medycyna, 1914, xlix, 990.
237. Czarkowsky: Medycyna, 1914, xlix, 985.
238. Keifer, G. L., and Ferry, N. S.: Med. Rec., New York, 1914, lxxxv, 1846.
239. Baginsky, A.: Abstr., Jahrb. f. Kinderh., 1913, lxxvi, 473.
240. Sexton, L. A.: Arch. Pediat., 1913, xxx, 360.
241. Wegmann: Abstr., Jahrb. f. Kinderh., 1913, lxxviii, 474.
242. Higgins, T. S.: Brit. Jour. Child. Dis., 1912, x, 418.
243. Jacobson: Arch. de méd. d. enfants, 1914, xvii, No. 4.
244. Döhle: Centralbl. f. Bakteriol., 1912, ??? 57.

bodies, which he described the year before. Kretschmer[245] found these bodies in all early cases of scarlet fever, but found them also in diphtheria and septic diseases. Glomset[246] found them often in health and obtained them artificially by shaking the blood. Schippers and de Lange[247] found them in all cases of scarlet fever, but also in other diseases, especially of streptococcal origin. They produced them by injecting dogs with this micro-organism. Bongartz[248] found them in typhoid, pneumonia and pertussis. Iskander Ahmed[249] found them in German measles. Nicoll,[250] however, missed them in this disease. Granger and Pale[251] missed them in the very severe cases of scarlet fever. They are not present in the so-called toxic rash. The value of these inclusion bodies in scarlet fever may be summed up by stating that they have only a negative diagnostic value; that is to say their absence speaks against a given rash being of scarlatinal origin. The Diazo reaction was suggested as a means of distinguishing between the serum rash and true scarlet fever. Woody and Kolmer[252] find that the Diazo reaction is as often positive in diphtheria as in scarlet fever and therefore is of no service. Schultz and Grote[253] used the Abderhalden method, hoping to determine whether a ferment with a specific action upon the scarlatinal lymph glands existed. They found that the ferments obtained were not specific for such glands, but would digest lymph gland tissues in general.

An interesting diagnostic test has been put forward by Umber.[254] Noting that urobilinogen appeared in the urine in many cases of scarlet fever, he suggested the use of an acid solution of paradimethylamidobenzaldehyde (Ehrlich's reagent) and found 96 per cent. positive results. Schelenz[255] verifies these findings and shows a section of an acute interstitial hepatitis. He emphasizes the fact that the test is valid only when done on the freshly passed urine. Hesse[256] also is of the opinion that the test is of value, and finds that it is necessarily coincident with the exanthem and that of course it can not be relied on alone for diagnosis. Gromski[257] determined the presence of urobilinogen by means of the spectroscope. He found it to vary with the tem-

245. Kretschmer: Deutsch. med. Wchnschr., 1912, xxxviii, 2163.
246. Glomset, D. L.: Jour. Infect. Dis., 1912, xi, 468.
247. Schippers and de Lange: Nederl. Tijdschr. v. Geneesk., 1913, 544.
248. Bongartz, H.: Berl. klin. Wchnschr., 1912, xlix, 2124.
249. Ahmed, Iskander: Berl. klin. Wchnschr., 1912, xlix, 1232.
250. Nicoll: Arch. Pediat., 1912, xxix, 350, 416; Ibib., 1913, xxx, 346.
251. Granger and Pale: Brit. Jour. Child. Dis., 1913, x, 9.
252. Woody and Kolmer: Arch. Pediat., 1912, xxix, 12.
253. Schultz, W., and Grote, L. R.: München. med. Wchnschr., 1913, lx, 2510.
254. Umber, F.: Med. Klin., 1912, viii, 322.
255. Schelenz, C.: Med. Klin., 1913, ix, 622.
256. Heese, O.: Med. Klin., 1913, p. 294.
257. Gromski: Abstr., Jahrb. f. Kinderh., 1914, lxxix, 383.

perature. Alimentary levulosuria could be produced by giving 40 to 60 gm. levulose. Jackobovicz[258] found the Wassermann reaction positive in eighteen out of fifty-five cases. It did not become positive, however, until the end of the third week and occurred most often in the severe cases. Michael[259] produced the so-called Rumpel-Lede phenomenon in 60 per cent. of healthy children by means of a blood pressure cuff, pressure of 60 mm. being applied for ten minutes. The spontaneous appearance of this phenomenon is discussed by Meyer,[260] who found it in all cases of scarlet fever, and in some cases of measles, sore throat and pernicious anemia. It was not found in German measles or erythema multiforme. Kirsch[261] is of the opinion that the rash of scarlet fever is due to the action of the toxin upon the muscular element of the capillaries and that, in given cases, the damage mav be of a more or less permanent character, leading to the so-called angioneuroses. In the disappearing scarlet fever eruption, he[262] finds at times that the tonus of the arteries and veins does not completely return to normal. During this period there are areas of pallor and also the appearance of persisting dilated capillaries. Hahn[263] discusses surgical scarlatina and finds a more intense rash, but a milder course with rare complications, to be the rule. The enanthem is either absent or, if present, is very slight only. The point of entrance of the virus is the face or the mouth.

Rolleston[264] has studied the blood pressure in scarlet fever and finds it to be subnormal in 25 per cent. of the cases, varying with the extent and duration of the initial attack. It is little over normal in the first week, but the reading diminishes toward the end of the disease. A very moderate hypertension, which is never extreme or of long duration, is occasionally encountered during the time of kidney complications. It may be concluded, therefore, that the systematic blood pressure readings are of little diagnostic or prognostic significance in themselves. The pronounced hypotension met with in adrenal insufficiency of course calls for adrenal medication. Pancreatitis as a complication of scarlet fever has been seen by Goldie.[265] In this series of four cases reported (one followed diphtheria) the pancreas was palpable. The symptoms were chiefly abdominal pain and tenderness, rigidity, tremor, jaundice, vomiting and general malaise. Tixier and

258. Jackobovicz, B.: Jahrb. f. Kinderh., 1914, lxxix, 215.
259. Michael, M.: Arch. Pediat., 1912, xxix, 298.
260. Meyer, O.: Deutsch. med. Wchnschr., 1912, xxxviii, 2019.
261. Kirsch, O.: Ztschr. f. Kinderh., 1912, iv, 92.
262. Kirsch, O.: Wien. klin. Wchnschr., xxvi, 1848.
263. Hahn, H.: Monatsch. f. Kinderh., 1913, xii, 233.
264. Rolleston, J. D.: Brit. Jour. Child. Dis., 1912, ix, 444.
265. Goldie: Lancet, London, 1912, No. 183, p. 1285.

Troisier[266] discuss the pathologic findings in the pancreas and the adrenal and call attention to the difficulty in definitely diagnosing the condition, pancreatitis, intra vitam; abdominal pain is a prominent symptom. In adrenal involvement abdominal or lumbar pain, cardiovascular collapse, and tachycardia are present.

Complications.—Several interesting complications are noted. Silberstein[267] reports a very rare complication—symmetrical gangrene of the skin. McCririck[268] reports a case of purpura fulminans developing nineteen days after the onset of the disease, with fatal termination. Stevenson[269] has a case of purpura hemorrhagica. Eichhorst[270] reports a case of complicating erythema nodosa. Riddell[271] reports a case of necrosis of the vertebra following scarlet fever. Gangrene of the sinus pyriformis has been encountered by Hecker.[272] Edgerly[273] discusses the joint complications in scarlet fever, with particular reference to the purulent form. The ear complications are discussed by Borden.[274] The middle ear is involved in 94 per cent. of fatal cases; the mastoid, in 26 per cent. Holmgren[275] does not find that the high mortality is necessarily associated with the percentage of otitis media. In his series only 33 per cent. of the patients in the fatal cases had otitis. After the second year the tendency to otitis diminished. This complication may develop without fever. He believes, however, that permanent perforations are present in 40 per cent. of all cases of otitis and that the hearing is affected in 73 per cent. The earlier the otitis develops the worse the prognosis, although the mastoid involvement tends to be associated more often with a late otitis. Children with adenoids have more serious results when the complication develops. He favors local treatment of the throat. The hospital at Stockholm has its own attending otologist for treatment of these patients.

Kalser and Lowy[276] have studied the variations in blood serum concentration. An increase in concentration has been noted in most cases and, therefore, is of no value in predicting nephritis. Fishbein[277] has used the functional test with phenolsulphonephthalein, but draws no definite conclusions as to the value in prognosis. Schridde[278] studied

266. Tixier and Troisier: Arch. de méd. d. enfants, 1912, xv, 321.
267. Silberstein, L.: Jahrb. f. Kinderh., 1912, lxxv, 350.
268. McCririck, R.: Brit. Jour. Child. Dis., 1912, No. 110, p. 154.
269. Stevenson, E. C.: West. Med. Rev., 1912, xvii, No. 3.
270. Eichhorst, H.: Med. Klin., 1914, x, 1045.
271. Riddell, D. F.: Glasgow Med. Jour., 1913, lxxviii, No. 6.
272. Hecker, T.: St. Petersb. Med. Ztschr., xxxvii, No. 18.
273. Edgerly, E. T.: Jour. Iowa State Med. Soc., 1912, ii, No. 3.
274. Borden, C. R. C.: Boston Med. and Surg. Jour., 1913, clxviii, 221.
275. Holmgren, G.: Otolaryngologiska, 1912; abstr., Jahrb. f. Kinderh., 1913, lxxviii, 485.
276. Kalser and Lowy: Deutsch. Arch. f. klin. Med., 1914, cxvi, 82.
277. Fishbein, M.: Jour. Am. Med. Assn., lxi, 1368.
278. Schridde, H.: Beitr. z. path. Anat. u. z. allg. Path., 1912, lv, 345.

the pathology of the kidneys in scarlatina and found that the characteristic changes consist in an enormous heaping up of lymphocytes in the capillaries of the medulla. Later, plasma cells, eosinophils and mast cells are found. There are no polymorphonuclears and no streptococci.

Several attempts have been made to prevent nephritis by dietary treatment. De Biehler[279] followed two groups of cases. In the first a milk diet was ordered, and but 2.4 per cent. developed nephritis, while among those given meat and mixed diet 5.3 per cent. showed this complication. Gerstley[280] comes to the opposite conclusion in following 306 patients, of whom half were given milk and one half mixed diet with meat. Not only were there no bad results, but the anemia so frequently following scarlet fever was prevented in part. Brückner[281] in 241 cases is also convinced of the fact that the diet does not play a part in the development of the disease. Bell[282] makes an interesting attempt in accordance with the idea of Fisher to prevent nephritis, namely, the administration of water and alkali in addition to the usual bed and dietary treatment. He used potassium citrate and sodium bicarbonate in the first ten days of the disease. Of 388 cases, but 2 per cent. developed this complication. The effectiveness of this treatment can be gaged by referring to the article of de Biehler.[283] Rosenfeld[284] examined ninety-three patients who had had scarlet fever, of whom fifty-two showed albuminuria at the time of discharge from the hospital. No single severe chronic nephritis was found. Orthostatic albuminuria was found in eight cases and twenty-eight showed a simple albuminuria. Formed elements in small number were found in but six cases.

Therapy.—The finding of a positive Wassermann test in a certain number of cases of scarlet fever has induced some observers to attempt the use of salvarsan for therapeutic purposes. Klemperer and Woita[285] administered this drug in sixty cases. The mortality was 8.3 per cent. Nephritis developed in 25 per cent. These figures speak for themselves. Glaser[286] used the drug in forty-two cases and found it to be of beneficial influence only in severe throat conditions, and a critical fall in temperature was observed at times. It has no influence on complications or on toxic cases. Lenzmann[287] treated forty-seven

279. De Biehler: Arch. de méd. d. enfants, 1912, xv, 759.
280. Gerstley, J. R.: Monatsch. f. Kinderh., 1913, xii, 121.
281. Brückner: Fortschr. d. Med., 1912, 1.
282. Bell, A. J.: Am. Jour. Med. Sc., 1912, cxliv, 669.
283. De Biehler: Arch. de méd. d. enfants, 1912, xv, 579.
284. Rosenfeld, J.: Ztschr. f. Kinderh., 1912, iv, 265.
285. Klemperer and Woita: Therap. d. Gegenw., 1912, liii, 198.
286. Glaser: Deutsch. med. Wchnschr., 1914, xl, 1760.
287. Lenzmann: Therap. d. Gegenw., 1914, lv, 243.

patients having scarlet fever in a severe form with neosalvarsan, of whom but two died. This was given intramuscularly daily or every second day. The dosage was from 0.15 gm. to 0.3 gm. for children. The maximum dose in three days was never over 0.8 gm.

Reiss and Jungmann[288] suggested the use of the serum of convalescents for treatment. The blood was obtained from scarlet fever patients during the third or fourth week. From 50 to 100 c.c. were given by intravenous injection in twelve cases with two failures, these being in a case of sepsis and in a case which turned out to be not scarlet fever. The ten cases were strikingly improved. The temperature fell within four hours, an average lowering of five degrees being attained. The pulse rate also became lower. It was most striking to see how delirious and toxic children would seem almost normal the morning after the injection. It had no effect, however, on secondary bacterial infections. Rowe[289] found no difference between serum obtained from patients who had not had scarlet fever and serum from convalescents. He used from 40 to 50 c.c. intravenously and his results were in the main confirmatory of those cited above. Moog[290] also found excellent results from human normal serum and believes that in the case of Moser's antistreptococcus serum the good effect obtained was due to the serum as such. Koch[291] reports twenty-two patients treated with convalescent serum by intravenous injections, 100 c.c. being used. Only bacterial complications were unaffected, while a beneficent influence on the disease was otherwise unmistakable. Barker,[292] apparently, independently of the above writers, used blood serum of immunes for the treatment in malignant septic cases. From 4 to 8 c.c. of the human serum hypodermically were given. No striking results were obtained. Prinzing[293] noted that horse serum was not a satisfactory substitute for human serum. The critical fall in temperature did not follow its use and the symptoms were not so strikingly affected. Schultz[294] found that the effect of human serum in scarlet fever was not due to the lipoid content, but with the non-treated serum, however, a critical fall in temperature could be produced. There are still some communications dealing with the use of the Moser serum. Schick[295] found some improvement produced in toxic patients, while those in whom the bacteria themselves produce the symptoms were unaffected. He believes that the failures hitherto

288. Reiss and Jungmann: Deutsch. Arch. f. klin. Med., 1912, cv, 70.
289. Rowe, C.: Med. Klin., ix, 1978.
290. Moog: Therap. Monatsh., 1914, p. 37.
291. Koch, R.: München. med. Wchnschr., 1913, lx, 2611.
292. Barker, W. S.: Arch. Pediat., 1914, xxxi, 599.
293. Prinzing, F.: Med. Klin., 1914, x, 931.
294. Schultz, W.: Deutsch. Arch. f. klin. Med., 1914, cxv, 627.
295. Schick, R.: Therap. Monatsh., 1912, xxvi, 258.

reported may have been due to the small dosage or to a weak serum. Lewkowicz[296] used an antistreptococcal serum in thirty cases, using twenty cases as controls. No effect was noted on the purely scarlatinal symptoms. The bacterial complications are not prevented, although they were surely improved. The Milne[59] treatment referred to under measles is commented on by Kretschmer,[297] who first calls attention to the fact that this method of treatment was first suggested by Curgenven in 1890. Kretschmer finds that it has little protective prophylactic value and did not prevent complications. Koerber[298] attempted to determine the efficiency of the Milne method by comparing the number of return cases, and he found there was no appreciable difference in the number. He is struck with the fact, however, that all complications in the eucalyptus series were less than in the controls. Only one half as many cases of nephritis developed in the treated series as in those nontreated. Schultze and Goldberger[299] used the vaccine treatment as well as the Milne treatment. Their figures are rather suggestive in homes where better conditions might have been expected. Of 354 controls, a mortality of 3 per cent. was encountered, whereas among 128 patients in the slums who were subjected to this treatment the mortality was but 1.5 per cent. Complications were also less frequently observed in the treated patients.

Langauer,[300] believing that the tonsils play an almost important rôle in scarlet fever, also believes in their local treatment. He used 10 per cent. hydrogen peroxid, 60 per cent. alcohol and 2 per cent. collargol in glycerin. When a membrane was present he removed this mechanically. Paoloantonia has found what seems to him a most efficient treatment for scarlatinal nephritis. In thirty cases the oral administration of from 10 to 20 drops of epinephrin (1 to 100) controlled the hematuria and edema and prevented the further development of the disease. Diuresis was increased and edema diminished.

296. Lewkowicz, X.: Monatschr. f. Kinderh., 1912, x, 676.
297. Kretschmer, M.: München. med. Wchnschr., 1912, lix, 1809.
298. Koerber: München. med. Wchnschr., 1912, lix, 581.
299. Schultze and Goldberger: Med. Rec., New York, 1914, lxxxv, 931.
300. Langauer, K.: Pest. med.-chir. Presse, 1913, p. 124.

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CORRECTION

In the July issue, p. 30, the heading "Electrocardiographic Studies of Congenital Heart Disease, Hugh McCulloch, Assistant in Pediatrics, George Washington University Medical School, Washington, D. C.," should have been "Assistant in Pediatrics, Washington University Medical School, St. Louis."